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

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groups of experts that provide WHO with the latest scientific and technical advice on
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serve without remuneration in their personal capacities rather than as representatives
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WHO Expert Committee on Biological Standardization

Seventy-eighth 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.
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WHO Expert Committee on Biological Standardization

Seventy-eighth meeting held using a hybrid format in which Committee members and the WHO Secretariat met in person in Geneva from 16 to 19 October 2023 with other participants attending virtually

Committee members¹

Dr S.S. Ben Amor, National Drug Control Laboratory, Tunis, Tunisia

Dr C. Burns, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

Professor K. Cichutek, Paul-Ehrlich-Institut, Langen, Germany (Co-chair)

Dr J.A. Dahlan, Directorate of Pharmaceutical, Narcotics, Psychotropics, Precursors and Addictive Substances Standardization, Jakarta, Indonesia

Dr S. Fakhrzadeh, Food and Drug Administration, Tehran, Iran (Islamic Republic of)

Dr I. Feavers, Consultant, Nacton, United Kingdom (Rapporteur)

Professor S. Hindawi, King Abdulaziz University, Jeddah, Saudi Arabia (Co-chair)

Professor M.B.C. Koh, St George’s Hospital Medical School, London, United Kingdom; and Health Sciences Authority, Singapore, Singapore (Co-rapporteur)

Dr Q. Meyer, South African National Control Laboratory for Biological Products, Bloemfontein, South Africa

Dr A. Ramkishan, Ministry of Health and Family Welfare, Hyderabad, India

Dr S. Silveira, Agência Nacional de Vigilância Sanitária, Brasilia, Brazil

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

Dr S. Wendel, Hospital Sirio-Libanês, São Paulo, Brazil

Dr T. Wisit, Ministry of Public Health, Nonthaburi, Thailand

Dr T. Wu, Health Canada, Ottawa, Canada

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.
Temporary advisors [in person]

Dr H. Meyer, Paul-Ehrlich-Institut, Langen, Germany
Dr T. Sithole, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe
Dr P. Stickings, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom
Dr A.L. Waddell, Consett, United Kingdom (Editor of the report of the Committee)

Temporary advisors [virtual]

Dr A.A. Alsayyari, Saudi Food and Drug Authority, Riyadh, Saudi Arabia
Dr A. Bisht, Ministry of Health and Family Welfare, Noida, India
Dr P. Boonprasirt, Food and Drug Administration, Nonthaburi, Thailand
Dr G. Cirefice, European Directorate for the Quality of Medicines & Healthcare, Strasbourg, France
Dr D. Darko, Food and Drugs Authority, Accra, Ghana
Dr J. Epstein, Chair of the ISBT Working Party on Global Blood and Safety; and Chair of the International Coalition for Safe Plasma Proteins
Dr M. Farouk, Africa Society for Blood Transfusion, Pinetown, South Africa
Dr A. Fouad, Egyptian Drug Authority, Cairo, Egypt
Dr Md. Harun-Or-Rashid, Directorate General of Drug Administration, Dhaka, Bangladesh
Dr A. Hilger, Paul-Ehrlich-Institut, Langen, Germany
Dr A. Holmes, National Centre for the Replacement, Refinement & Reduction of Animals in Research, London, United Kingdom
Dr M. Li, National Medical Products Administration, Beijing, China
Dr E. Lilley, National Centre for the Replacement, Refinement & Reduction of Animals in Research, London, United Kingdom
Dr L. Mallet, European Directorate for the Quality of Medicines & Healthcare, Strasbourg, France
Dr C. Morris, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom
Dr K. Quillen, Harvard Medical School, Boston, MA, United States of America (USA)
Dr R. Siggers, Health Canada, Ottawa, Canada

2 Unable to attend.
Dr C. So-Osman, Sanquin Blood Supply, Amsterdam; and Erasmus Medical Center, Rotterdam, Netherlands (Kingdom of the)

Dr D. Teo, Visiting Consultant, Blood Services Group, Health Sciences Authority, Singapore, Singapore

Dr M. Wierer, European Directorate for the Quality of Medicines & Healthcare, Strasbourg, France

Dr C. Witten, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

**State actors [virtual]**

Dr N. Almond, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

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

Dr S. Baylis, Paul-Ehrlich-Institut, Langen, Germany

Dr E. Bentley, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

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

Dr C. Cherry, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

Dr B. Cowper, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

Dr A. Eder, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Dr O. Engelhardt, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

Dr E. Griffiths, Consultant, Kingston upon Thames, United Kingdom

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

Dr J. Hogwood, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

Dr K. Ishii, National Institute of Infectious Diseases, Tokyo, Japan

Dr A. Ishii-Watabe, National Institute of Health Sciences, Kawasaki, Japan

Dr A. Khan, US Food and Drug Administration, Silver Spring, MD, USA
Dr P. Marks, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Dr J. Martin, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

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

Dr M. Nübling, Paul-Ehrlich-Institut, Langen, Germany

Dr M. Ochiai, National Institute of Infectious Diseases, Tokyo, Japan

Dr K. Partridge, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

Dr G. Raychaudhuri, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Dr N. Rose, Medicines and Healthcare products Regulatory Agency, Potters Bar, 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, Chungcheongbuk-do, Republic of Korea

Dr C. Schärer, Swiss Agency for Therapeutic Products, Bern, Switzerland

Dr C. Scott, Department of Health and Aged Care, Woden ACT, Australia

Dr C. Sergaki, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

Dr I. Shin, Ministry of Food and Drug Safety, Chungcheongbuk-do, Republic of Korea

Professor C.T. Tagny, Haematology and Blood Transfusion Service, University Teaching Hospital, Yaoundé, Cameroon

Dr Y. Takahashi, National Institute of Infectious Diseases, Tokyo, Japan

Dr C. Thelwell, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

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

Dr M. Valadkhani, Food and Drug Administration, Tehran, Iran (the Islamic Republic of)

Ms B. Valente, Agência Nacional de Vigilância Sanitária, Brasilia, Brazil

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

Dr J. Weir, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA
Dr H. Wilmot, Medicines and Healthcare products Regulatory Agency, Potters Bar, United Kingdom

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

**Observers from non-state actors in official relations**

*International Alliance of Biological Standardization*
Dr R. Sheets

*International Federation of Pharmaceutical Manufacturers & Associations*
Dr M. Gencoglu, Geneva, Switzerland

*International Generic and Biosimilar Medicines Association*
Dr S. Kox, Washington, DC, USA

*International Society of Blood Transfusion*
Dr D. Candotti, Créteil, France

*International Union of Immunological Societies*
Dr L. Andrade, Brazil

*Pharmaceutical and Medical Device Regulatory Science Society of Japan*
Dr Y. Nakagawa, Osaka, Japan

*United States Pharmacopeial Convention*
Dr F. Atouf, Rockville, MD, USA

**Intergovernmental organizations**

*European Medicines Agency*
Dr E. Pedone, Amsterdam, Netherlands (Kingdom of the)

**Representation from other entities**

*Africa Society for Blood Transfusion*
Dr M. Farouk, Cairo, Egypt

*Biotechnology Innovation Organization*
Dr D. Scholes, Washington, DC, USA

*Coalition for Epidemic Preparedness Innovations*
Dr P. Kristiansen, Oslo, Norway

*Developing Countries Vaccine Manufacturers Network*
Dr S. Gairola, India

*Plasma Protein Therapeutics Association*
Dr D. Misztela, Brussels, Belgium
WHO Expert Committee on Biological Standardization
Seventy-eighth report

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

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

WHO Secretariat
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)
Mr S. Chatzixiros
Ms S. Jenner
Dr H-N. Kang
Dr E. Kim
Dr D. Lei
Dr J. Yu
Dr T. Zhou

Other WHO staff
Dr R. Balocco (MHP/INN)
Dr A. Aceves Capri (MHP/HPS/ATM/MDD)
Dr L. Gwaza (TSS/NSP)
Dr J. Hombach (UHL/IVB/APS)
Dr B. Huttner (MHP/EML)
Dr A. Khadem (MHP/RPQ)
Dr R. Ostad Ali Dehaghi (MHP/RPQ)

Representation from WHO regional offices
WHO Regional Office for Africa
Dr N. Menasria

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

WHO Regional Office for South-East Asia
Dr A. Chawla
Dr A. Inoubli
Dr A. Singh
WHO Regional Office for Europe
Dr D. Pirgari

WHO Regional Office for the Eastern Mediterranean
Dr H. Langar

WHO Regional Office for the Western Pacific
Dr J. Shin
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<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>3Rs</td>
<td>Replacement, Reduction and Refinement (of use of animals in research)</td>
</tr>
<tr>
<td>AFP</td>
<td>alpha-fetoprotein</td>
</tr>
<tr>
<td>AG-BRAS</td>
<td>Advisory Group for Blood Regulation, Availability and Safety</td>
</tr>
<tr>
<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
</tr>
<tr>
<td>CCP</td>
<td>COVID-19 convalescent plasma</td>
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<tr>
<td>COVID-19</td>
<td>coronavirus disease 2019</td>
</tr>
<tr>
<td>C-STFT</td>
<td>Committee for the Standardization of Thyroid Function Tests</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>ECSPP</td>
<td>WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
</tr>
<tr>
<td>EDL</td>
<td>WHO Model List of Essential In Vitro Diagnostics</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines &amp; HealthCare</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EML</td>
<td>WHO Model List of Essential Medicines</td>
</tr>
<tr>
<td>EMLc</td>
<td>WHO Model List of Essential Medicines for children</td>
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<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
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<tr>
<td>FVIII</td>
<td>blood coagulation factor VIII</td>
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<tr>
<td>GCV</td>
<td>geometric coefficient of variation</td>
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<tr>
<td>HDFN</td>
<td>haemolytic disease of the fetus and newborn</td>
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<tr>
<td>HEV</td>
<td>hepatitis E virus</td>
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<tr>
<td>HTS</td>
<td>high-throughput sequencing</td>
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<tr>
<td>IFA</td>
<td>immunofluorescence assay</td>
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<tr>
<td>IFCC</td>
<td>International Federation of Clinical Chemistry and Laboratory Medicine</td>
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<tr>
<td>INN</td>
<td>international nonproprietary name(s)</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>ISA</td>
<td>WHO international standards for antibiotics</td>
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<tr>
<td>Acronym</td>
<td>Term</td>
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<tr>
<td>ISBT</td>
<td>International Society of Blood Transfusion</td>
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<tr>
<td>ISI</td>
<td>International Sensitivity Index</td>
</tr>
<tr>
<td>IVD</td>
<td>in vitro diagnostic</td>
</tr>
<tr>
<td>LH</td>
<td>luteinizing hormone</td>
</tr>
<tr>
<td>LMIC</td>
<td>low- and middle-income countries</td>
</tr>
<tr>
<td>mAb</td>
<td>monoclonal antibody</td>
</tr>
<tr>
<td>MAPREC</td>
<td>mutant analysis by PCR and restriction enzyme cleavage</td>
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<td>MHRA</td>
<td>Medicine and Healthcare products Regulatory Agency, UK</td>
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<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
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<td>MTT</td>
<td>manual tilt tube</td>
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<td>NC3Rs</td>
<td>National Centre for the Replacement, Reduction and Refinement of Animals in Research</td>
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<tr>
<td>NCL</td>
<td>national control laboratory</td>
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<tr>
<td>NiV</td>
<td>Nipah virus</td>
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<tr>
<td>NRA</td>
<td>national regulatory authority</td>
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<tr>
<td>nOPV</td>
<td>novel oral poliomyelitis vaccine</td>
</tr>
<tr>
<td>ODP</td>
<td>WHO INN Open Database for Proteins</td>
</tr>
<tr>
<td>OPV</td>
<td>oral poliomyelitis vaccine</td>
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<tr>
<td>PDMP</td>
<td>plasma-derived medicinal product</td>
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<tr>
<td>PEI</td>
<td>Paul-Ehrlich-Institut</td>
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<tr>
<td>PT</td>
<td>prothrombin time</td>
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<tr>
<td>RhD</td>
<td>rhesus D</td>
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<tr>
<td>RRV</td>
<td>Ross River virus</td>
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<tr>
<td>RSV</td>
<td>respiratory syncytial virus</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>SSC/ISTH</td>
<td>Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis</td>
</tr>
<tr>
<td>TAFI</td>
<td>thrombin activatable fibrinolysis inhibitor</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid-stimulating hormone</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>VOC</td>
<td>variant(s) of concern</td>
</tr>
<tr>
<td>VWF</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>VIFFP</td>
<td>virus inactivated fresh frozen plasma</td>
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<td>WHOCC</td>
<td>WHO collaborating centre</td>
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1. Introduction

The seventy-eighth meeting of the WHO Expert Committee on Biological Standardization was held from 16 to 19 October 2023 as a hybrid meeting, with Committee members attending in person at WHO headquarters in Geneva and others participants attending virtually. Dr Yukiko Nakatani, Assistant Director-General, Access to Medicines and Health Products, welcomed all participants and thanked them for devoting their time and expertise to the work of the Committee. Noting that the frequency of Committee meetings had increased to meet increasing demands for new and replacement standards for biological products, including products used during public health emergencies, Dr Nakatani remarked that this 78th meeting of the Committee was taking place in the same year that WHO celebrated its 75th anniversary. Dr Nakatani also highlighted the 57th meeting of the Expert Committee on Specifications for Pharmaceutical Preparations, which had met in the previous week, and the 77th consultation on International Nonproprietary Names, which was taking place at the same time as the current meeting (see sections 2.3.1 and 2.3.4 respectively).

Dr Nakatani then drew attention to the commitment of WHO to provide support to its Member States in expanding access to essential medicines. The importance of the work of WHO in providing countries with world-class, evidence-based norms, standards, research and data, along with much needed technical and operational support, had been explicitly highlighted by the Director-General of WHO during the Executive Board meeting held in January. In the context of responding to public health emergencies, Dr Nakatani noted that the coronavirus disease 2019 (COVID-19) pandemic had reinforced the need for equitable access to medicinal products for all, and the outputs of this Committee, especially the WHO written and measurement standards, would help to improve equitable access to biological products of assured quality, safety and efficacy, especially in low and middle-income settings. Dr Nakatani also highlighted the crucial importance of ongoing efforts with regard to polio eradication, and specifically the work being done to ensure the availability of safe and standardized polio vaccines. When the Global Polio Eradication Initiative was established in 1988, there were an estimated 350 000 cases a year. This year, a total of nine cases of wild poliovirus had been reported, and the world was now on the threshold of making polio only the second human disease in history to be eradicated. An update on the development of WHO international standards for polio vaccines would be presented later in this meeting (see section 9.2.2 below).

In the context of current WHO planning activities for the 2024–2025 biennium and for its Global Programme of Work for 2025–2028, Dr Nakatani welcomed the upcoming discussions of the Committee on the continuing development, establishment and distribution of WHO written
and measurement standards for biological products. Such discussions and the resulting recommendations of the Committee are both timely and vital in ensuring that such WHO standards remain current and fit for purpose, and that newly emerging biological standardization needs are addressed. Noting the full agenda of the Committee, Dr Nakatani welcomed the proposed WHO Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries, as well as the range of WHO measurement standards being proposed for endorsement or establishment at the current meeting.

Dr Nakatani concluded by expressing her gratitude for the active participation of all the key WHO stakeholders present. The world needs WHO more than ever, and WHO in turn relies on the expertise of its expert committees and other entities to support its global health leadership. Specifically, the contributions of the Committee continue to be vital in helping WHO to maintain the delicate balance required when making timely, relevant, inclusive and science-driven recommendations to countries, and to the broad range of international organizations and other stakeholders that rely on WHO standards.

Dr Ivana Knezevic, Secretary to the Committee, thanked Dr Nakatani for her opening remarks. Welcoming Committee members, Dr Knezevic went on to note that, as the directing and coordinating authority on international health within the United Nations system, the values of WHO were consistent with the United Nations principles of respect for human rights, diversity and equity established in its constitution. As the decision-making body of WHO, the World Health Assembly is attended by delegations from all WHO Member States, and sets the international health agenda – with support from the Executive Board, to which the reports of this Committee are presented. Dr Knezevic noted that two World Health Assembly resolutions of particular relevance to the work of the Committee had been passed on regulatory strengthening (WHA67.20) and on access to biotherapeutic products, including biosimilars (WHA67.21). Through its activities at headquarters, regional office and country office level, WHO as part of its core functions sets international norms and standards for such products, while also working to ensure their implementation worldwide.

Dr Knezevic noted that several new Committee members were present and went on to explain that all Committee members were drawn from the WHO Expert Advisory Panel, which itself was being expanded to provide the necessary expertise to cover the increasing scope of biological standardization, and the resulting expansion in the work of the Committee. However, it would also be important to continue to ensure the continuity of the membership of the Committee from one meeting to the next. Dr Knezevic continued by outlining the procedures and working arrangements of the meeting. A short open information-sharing session involving all participants, including non-state actors, would be held on Monday 16 October 2023. Committee members, regulatory
authority representatives and subject matter experts from governmental organizations would then participate in the main meeting. 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 on Thursday 19 October 2023 attended only by Committee members and the WHO Secretariat. Dr Knezevic concluded by thanking all participants for their continued efforts and commitment to the work of the Committee.

In the absence of dissent, Professor Klaus Cichutek and Dr Salwa Hindawi were elected as Co-chairs. Dr Ian Feavers and Professor Mickey Koh were elected as Rapporteur and Co-rapporteur respectively. Dr Knezevic presented the declarations of interests provided by Committee members, WHO temporary advisers and other participants. Following evaluation, WHO had concluded that none of the interests declared constituted a significant conflict of interest and that everyone could participate fully in the meeting.

The Committee then adopted the proposed agenda (WHO/BS/2023. 2465).
2. General

2.1 Current directions

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

Dr Knezevic provided meeting participants with an overview of recent and planned WHO activities in the above areas, with a specific focus on the ever-increasing number of WHO written and measurement standards. Based on scientific evidence, these resources were essential in the development, regulatory approval and quality control of a broad range of biological products. In the case of written standards for vaccines, such standards could be divided into those broadly applicable to all vaccines and those that were vaccine specific. Examples of the latter included the WHO written standards recently developed on plasmid DNA and messenger RNA (mRNA) vaccines during the COVID-19 pandemic. Recognizing the crucial role of WHO collaborating centres (WHOCCs) and custodian laboratories in the drafting of such written standards, the production of WHO measurement standards and the conducting of supporting implementation workshops, Dr Knezevic was pleased to inform the Committee that the redesignation of WHOCCs was back on track following the pandemic – though a proposed meeting of the WHOCC network of collaborating centres on standardization and regulatory evaluation of vaccines had been postponed until 2025.

Dr Knezevic went on to summarize of the principal outcomes of the 76th and 77th meetings of the Committee, and to provide an update on the status of recent and upcoming WHO written standards. Following the adoption of the WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases at the previous meeting of the Committee, a number of disease-specific addenda were now being developed, including an addendum specifically on monoclonal antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Preparations were also being finalized for an implementation workshop on the WHO manual for the preparation of reference materials for use as secondary standards in antibody testing – again, with a focus on SARS-CoV-2 standards. During the current meeting, the WHO Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries would also be considered for adoption (see section 3.1.1 below). Other WHO written standards currently undergoing revision included the WHO Guidelines on procedures and data requirements for changes to approved vaccines, and the WHO Guidelines to assure the quality, safety and efficacy of live attenuated rotavirus vaccines (oral) – both of which were expected to be presented to the Committee for consideration in October
2024. With regard to the former document, Dr Knezevic summarized the main outcomes of a meeting recently hosted by the Paul-Ehrlich-Institut which would be used to inform and help streamline the revision process.

Dr Knezevic went on to highlight the benefits of holding biannual meetings of the Committee but also noted the associated time and other resource pressures placed on the delivery of new and revised WHO written standards – necessitating a process of prioritization. Dr Knezevic summarized the WHO written standards scheduled for revision, development and implementation from 2024 onwards. Documents for revision would likely include vaccine-specific WHO written standards on yellow fever vaccines, dengue vaccines, measles, mumps and rubella vaccines, bacillus Calmette-Guérin (BCG) vaccines and malaria vaccines. Upcoming revision was also scheduled of more general documents on vaccine lot release, and of the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards. Newly developed documents for the standardization of enteric vaccines would also likely be needed. Implementation workshops on poliomyelitis vaccines, the above-mentioned manual on secondary standards, cell, tissue and gene therapy products, and biosimilars were all scheduled between now and July 2024. Dr Knezevic invited the views of the Committee on these and other envisaged requirements for future WHO written and measurement standards in light of the advances now being made in several areas. Dr Knezevic then indicated that the Committee would also be asked for its advice on the response of WHO to the report commissioned from the National Centre for the Replacement, Reduction and Refinement of Animals in Research (NC3Rs) in the United Kingdom on animal testing requirements currently cited in WHO written standards. This report would be presented in full to the Committee for its consideration during the current meeting (see section 3.1.2 below). The Committee was also briefly apprised of ongoing efforts to rationalize and archive the current set of WHO written standards for all biological products. It was envisaged that the approximately 110 current written standards would be reduced to around 90 in the coming months, with any discontinued guidelines archived to provide an historical record.

Reflecting on the issue of resources, the Committee commended WHO for the volume of work undertaken to develop timely guidance on biological products for use during the COVID-19 pandemic, and encouraged WHO to make full use of external experts, WHOCCs and other subject matter experts. The Committee went on to suggest specific needs for new or revised WHO guidance, including on the evaluation of chikungunya and rotavirus vaccines. The Committee also suggested that a single revised WHO guidelines document on post-approval changes might usefully incorporate guidance covering both vaccines and biotherapeutics, given the similarity of issues in these product areas. In conclusion, the Committee reflected on the need for further guidance
for NRAs in the area of cell, tissue and gene therapy products, and was assured that WHO planned to reconvene the working group that had been specifically established to address this subject.

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 the Advisory Group for Blood Regulation, Availability and Safety (AG-BRAS). Under its new Chair and Co-Chair, the workplan for 2023–2025 included revision of the current WHO guidelines on good manufacturing practices for blood establishments. In addition, in collaboration with the International Society of Blood Transfusion (ISBT) working party on transfusion medicine, a position paper will be developed on the collection and use of convalescent plasma and hyperimmune immunoglobulins against SARS-CoV-2 and future pandemic viruses. Policy considerations in the exportation of domestic plasma to obtain plasma-derived medicinal products (PDMPs) would also be produced, with support in this and other areas provided to countries through the WHO-ISBT Achilles Project.

Challenges facing blood services in many countries include a lack of regulation, an inadequate blood supply (including during emergencies), poor quality control, limited access to PDMPs and poor clinical practice. The WHO Action framework to advance universal access to safe, effective and quality-assured blood products was launched in 2020 to address these and other challenges through the delivery of its five strategic objectives. Implementation of the Action framework had recently focused on identifying barriers in blood services using the blood system self-assessment (BSS) tool. Dr Mohammed Farouk provided the Committee with a detailed overview of the development, structure and objectives of the BSS tool following numerous requests from countries for WHO to provide practical guidance and tools in this area. Aligned with the principles and general structure of the WHO Action framework, the tool is intended to help countries assess their blood systems using a step-wise questionnaire to identify strengths and challenges in moving toward a well-functioning blood system. The tool also provides guidance on actions that might strengthen a given blood system. Dr Farouk concluded by summarizing a number of caveats and practical considerations when using the tool.

Dr Maryuningsih went on to note that ensuring access to safe plasma protein products remained a particular challenge in low-and middle-income countries (LMIC). WHO is now helping countries to address this challenge through the revived Achilles Project, which focuses on improving the quality and safety of blood products, while avoiding wasting plasma that could be used for the fractionation of PDMPs. This work was part of a formal 5-year collaboration between WHO and ISBT, and Dr Jay Epstein, chair of the ISBT Working Party on
Global Blood Safety, elaborated on the origin and objectives of the WHO-ISBT Collaboration Agreement. A key element of this agreement was the provision of support by ISBT for WHO activities through its role as both member and host of the International Coalition for Safe Plasma Proteins which represents blood and plasma donors, patients with bleeding disorders or immunodeficiencies, blood establishments and plasma fractionators. The specific aims of the agreement include supporting the introduction of production technologies for safe plasma protein products and tailored fractionation approaches in LMIC, facilitating their implementation and sustainability, and empowering LMIC to resolve supply issues and shortages of safe products. Key components in increasing supplies of PDMPs in LMIC through fractionation of domestic plasma will be the stepwise development of local product preparation, together with capacity-building at the national level and the establishment of competent blood regulation.

Dr Maryuningsih went on to highlight a range of challenges facing the Achilles project. These include poor awareness of plasma wastage among governments and regulatory authorities, a lack of blood regulation for the production of safe plasma protein products, inexperience in the quality control and safety of PDMPs, a reluctance to export plasma for contract plasma fractionation, and poor awareness among clinicians of the potential use of PDMPs made from domestic plasma. In addition, the inclusion of pathogen-reduced cryoprecipitate in the latest WHO Essential Medicines List highlighted the fundamental importance of this product. In this context, recent WHO-ISBT agreement activities had included a pilot project on the preparation of pathogen-reduced cryoprecipitate at the National Blood Transfusion Centre in Dakar, Senegal, and a project in Indonesia on the preparation of plasma to be fractionated abroad under contract, supported by educational materials and training for clinicians on the use of PDMPs. Dr Maryuningsih concluded by summarizing other recent WHO activities relating to blood products and in vitro diagnostics (IVDs), and by outlining the range of WHO international reference standards in this area proposed for consideration at the current meeting.

The Committee commended both WHO and AG-BRAS for the excellent efforts being made in this area. Commenting on the development of the BSS tool, the Committee agreed that although it could not be used for comparing countries given differences between national arrangements and the charitable nature of blood donation worldwide, its strength would lie in producing helpful guidance. Despite potential concerns regarding its validation, the successful use of the tool in Ghana had demonstrated its ability to identify the strengths and weaknesses of a blood system, and to trigger much needed conversations among relevant parties on prioritizing improvements. While commenting that additional refinements may be identified with further use, the Committee acknowledged that the tool reflected the strategic objectives set out in the WHO Action framework.
2.1.3 **Update on COVID-19 standardization activities**

Dr Eunkyung Kim reminded meeting participants of the recent adoption of two WHO written standards on monoclonal antibodies (mAbs). The first of these had been the WHO Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use, regardless of therapeutic application or biosimilarity. This had then been followed by the adoption of the WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases. During the adoption of the latter document, the Committee had been informed of an intention to produce a number of disease-specific addenda as required. Dr Kim updated the Committee on the progress being made in developing an addendum on the nonclinical and clinical evaluation of mAbs and related products specifically intended for the prevention or treatment of COVID-19.

Dr Kim noted that mAbs are now the largest class of therapeutic proteins and that the development of a treatment for SARS-CoV-2 infection was considered to be a high priority. As had been highlighted by the COVID-19 pandemic, their short development time, rapid impact and good safety characteristics make mAbs a key option for use during public health emergencies. To date, six mAbs had been licensed or approved for emergency use against SARS-CoV-2, with many more now in development. SARS-CoV-2 continued to pose a major threat and to spread widely, causing severe disease and in some cases long COVID. Evidence indicates that it has become endemic, resulting in hospitalizations and deaths as new variants emerge. In addition, there remains cause for concern among vulnerable groups, including the immunocompromised and those with underlying comorbidities. However, access to mAbs is largely restricted to high-income countries, with their poor availability in LMIC attributed to the challenging regulatory environment, cost, manufacturing capacity and restrictive health policies. The WHO guidance now under development was intended to help address regulatory and related challenges, and Dr Kim outlined in detail the structure of the prospective addendum, its development plan and timelines. It was anticipated that the resulting document would be presented to the Committee for its consideration in March 2024. Future infectious disease addenda were also planned and would cover mAbs used to prevent or treat disease caused by respiratory syncytial virus (RSV), rabies virus, malaria and human immunodeficiency virus (HIV).

Dr Cynthia So-Osman then updated the Committee on the ongoing project to evaluate the use of convalescent plasma and hyperimmune immunoglobulin in the treatment of COVID-19. Based on the most recent Cochrane living systemic reviews, together with a literature review, the presentation reflected a further year of data since the last update. The Committee
was reminded that the current emergency use authorization issued by the United States Food and Drug Administration only permitted the use of high-titre COVID-19 convalescent plasma (CCP) early in the disease course and did not authorize the use of low-titre plasma. Noting that more recent studies had used 2–4 plasma units compared to the 1–2 units used in older studies, Dr So-Osman reported that two new outpatient studies, 15 new hospitalized patient studies and a further hyperimmune immunoglobulin study had been added to the previous results. The outpatient studies had indicated no difference in 28-day mortality when compared with either placebo or standard plasma, although there was a slight reduction in hospital admissions and the use of oxygen. Studies conducted in hospitals similarly indicated that CCP had no impact on the 28-day mortality outcome, and that there was no difference between groups with moderate and severe disease. One of the studies had included a 180-day mortality follow up, which again indicated no difference between inpatient and control groups. All the studies had monitored adverse reactions, with the resulting data suggesting that treatment with CCP was safe. Despite continued interest in the efficacy of CCP and hyperimmune immunoglobulin use among immunosuppressed patients, the evidence for this patient group remained inconclusive due to insufficient participant numbers, and despite newly available data. The outcomes of two large randomized controlled trials (REMAP-CAP and COVIC-19) to evaluate CCP use in immunosuppressed patients are awaited.

During discussion, the Committee highlighted a number of issues for consideration during the finalization of the COVID-19 mAb addendum, including the need to monitor the performance of mAbs against variants of concern (VOC) during nonclinical and clinical studies, and the need to discuss the complexities involved in performing bridging studies with the decision-making NRA. The Committee further suggested that consideration also be given to providing guidance on streamlining nonclinical and clinical studies during emergency situations, on alternative routes of administration, and on the use of mAbs in vulnerable groups. Reflecting on the timelines presented for developing disease-specific addenda, the Committee recognized the urgent need for the COVID-19 document but suggested that the proposed addendum on HIV be assigned a higher priority to support ongoing product development. In response, it was noted that a number of broadly applicable overarching principles were already set out in the Guidelines on the nonclinical and clinical evaluation of mAbs. The Committee looked forward to its further consideration of the COVID-19 addendum at its next meeting.

Commenting also on the importance of the ongoing studies into the use of CCP and hyperimmune immunoglobulin, the Committee enquired if endpoints other than all-cause mortality at day 28 might be considered in the analysis. Dr So-Osman explained that although the studies reported various clinical outcomes most included mortality at 28 days allowing them to be included.
The Committee went on to discuss the impact of changes in the prevalent VOC over the timeframe of a study, and concluded that CCP was more likely to contain antibodies to recently circulating VOC than hyperimmune immunoglobulin, which takes longer to produce. Reflecting on the successful use of convalescent plasma to treat other diseases, the Committee acknowledged the need to understand why this approach appeared to be unsuccessful for COVID-19. It was speculated that this might be attributable to the antigenic diversity of VOC or to the inability to administer CCP early enough in the course of infection. While questioning the likely benefit of the proposed position paper when CCP appears to be ineffective, the Committee accepted that evidence may yet emerge to support the use of CCP in immunocompromised patients. In addition, guidance on exploring the potential use of convalescent plasma in general might still be useful even if the use of CCP was not authorized.

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, USA

Dr Jerry Weir reviewed the recent vaccine-related activities of CBER, which focused on the development and use of high-throughput sequencing (HTS) technologies as a replacement for animal testing for adventitious virus detection. Dr Weir explained how the HTS approach was underpinned by a publicly available and recently updated and refined CBER reference virus database hosted by the University of Delaware, and highlighted the proposed WHO international reference panel to be discussed at the current meeting (see section 7.2.1 below).

Dr Weir went on to list several international collaborative studies in which CBER was participating, including a project led jointly with the Medicines and Healthcare products Regulatory Agency (MHRA) to replace the neurovirulence testing of poliomyelitis vaccines with whole-genome HTS. In addition, CBER was currently involved in the revision of two vaccine-related WHO guidelines – one on rotavirus vaccines and the other on post-approval changes. Looking ahead, CBER anticipated that reference materials were likely to be required to harmonize assays for biomarkers intended for monitoring disease progression and/or treatment response during hepatitis B virus infection. The further development of HIV-1 reference materials was also under consideration.

Dr Weir then made a number of suggestions for future standardization activities, including the need to support the application of the 3Rs principles (Replacement, Reduction and Refinement), including through implementation of new technologies to reduce animal testing, and in light of the NC3Rs report that would be presented to the Committee at this meeting (see section 3.1.2
below). CBER support was expressed for the establishment of a working group to review the actions arising from this report and to leverage its findings. This could include the development of a specific WHO guidance document outlining the 3Rs principles and their supporting scientific evidence. Other future activities should include the holding of implementation workshops for the recently published WHO guidance document on developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products to support countries and improve access to such treatments, particularly in LMIC. Dr Weir concluded by noting the involvement of CBER in a number of WHO measurement standards to be considered for establishment at the current meeting and indicating the willingness of CBER to participate in the development of a number of upcoming WHO written standards and associated activities.

**European Directorate for the Quality of Medicines & HealthCare (EDQM), Strasbourg, France**

Dr Laurent Mallet began by noting that, since 2006, EDQM had been the custodian laboratory of the 23 WHO international standards for antibiotics (ISA), with 10–20 vials of each ISA being distributed annually. No issues had been identified since the previous meeting of the Committee and no replacement ISAs were anticipated for at least 2 years.

Dr Mallet then updated the Committee on a collaborative study on the standardization of an enzyme-linked immunosorbent assay (ELISA) for use as an in vitro alternative to the current in vivo assay for the potency testing of human rabies vaccines. A quantitative sandwich ELISA based on two well-characterized neutralizing mAbs had been chosen for evaluation and had been shown to discriminate between potent and subpotent vaccine lots, and to recognize most of the virus strains used in human rabies vaccines. Study participants had now reported similar potency estimates, satisfactory assay precision, and low intra- and inter-laboratory variation. Despite some suboptimal method transfer during the COVID-19 pandemic, the data suggest that the method has the potential to replace animal-based potency tests for human inactivated rabies vaccines. Data from ongoing work would shortly be used to inform the setting of specifications and assay validity criteria, with a view to replacing the in vivo potency assay in Europe by 2025.

Dr Mallet also updated the Committee on progress made towards animal-free pyrogen testing in Europe by 2025. An international conference jointly hosted by EDQM and the European Partnership for Alternative Approaches to Animal Testing had been held in February 2023 attended by 250 participants from industry, academia, NRAs, national control laboratories (NCLs) and assay manufacturers. During the meeting it was noted that progress in phasing out the rabbit pyrogen test worldwide was being hampered by a lack of information on alternative methods. Recognizing the crucial need for standardized reagents
and kits for implementing the in vitro monocyte activation test, conference participants had highlighted the importance of international convergence in progressing towards animal-free pyrogen testing globally.

Dr Mallet concluded by highlighting a number of European Pharmacopoeia texts that anticipate the use of HTS and other molecular approaches to test for adventitious viruses in biological products. A general chapter specifically on HTS was also currently being developed by the European Pharmacopoeia HTS Working Party. During discussion of this development, and of the similar intention to develop a WHO written standard on HTS, it was noted that the Committee would be well placed to ensure the consistency of these two resources. The Committee commended the efforts of EDQM to replace animal testing wherever possible.

**Medicines and Healthcare products Regulatory Agency (MHRA), Potters Bar, United Kingdom**

Dr Marc Bailey updated the Committee on recent and planned standardization activities at the MHRA and began by outlining the MHRA annual report for the period July 2022 to June 2023. MHRA serves as the custodian laboratory for more than 400 WHO measurement standards, and in this context Dr Bailey presented a list of upcoming collaborative studies, including estimated launch dates. This list would be published on the WHO website to ensure that all stakeholders have a clear sense of forthcoming WHO measurement standards, and of the collaborative studies that would underpin their development. It was intended that publicizing this information would lead to increased interest from potential study participants – though participant numbers would have to be balanced against the study needs and the resources required to manage the logistics. A total of 29 such studies were expected to start before the end of 2024. Dr Bailey then summarized the status of all 110 projects on the MHRA database endorsed by the Committee, most of which were for new rather than replacement reference materials. Ongoing review was taking place of a number of these projects currently on hold, with a decision already having being made not to proceed with three WHO international reference reagents for MAPREC now that HTS had been validated as a better alternative technology. In addition, MHRA would be proposing the formal discontinuation of the First WHO International Standard for human C-reactive protein during the current meeting (see section 6.2.2 below).

Dr Bailey also briefly reported on discussions at a recent International Alliance of Biological Standardization Vaccine Standards Meeting concerning the impact on manufacturers when a primary standard is replaced – potentially causing a shift in vaccine potency estimates. Internal MHRA discussions were being held to consider whether collaborative studies could be designed to identify and minimize any such impact.
The Committee noted that the list of new and replacement measurement standards proposed by MHRA was ambitious, and that support from WHO and other WHOCCs might be beneficial. The Committee commended the intention to publish and update the list of upcoming standards projects on the WHO website as this would increase their visibility among stakeholders, while also encouraging wider participation in the collaborative studies.

The Committee clarified that the procedure for the discontinuation of existing WHO international standards was initiated by publication of a proposal for public consultation. After reviewing the rationale for the discontinuation, and the comments received from interested parties during the consultation process, the Committee would make its decision at a subsequent meeting. MHRA agreed that a number of ampoules of any such discontinued standard would be archived for use in possible future collaborative studies. The Committee also clarified that the case for not proceeding with a previously endorsed project proposal should similarly be presented for its consideration. In both cases, a one-page proposal outlining the rationale and potential impact on stakeholders should be presented to the Committee for approval.

**Paul-Ehrlich-Institut (PEI), Langen, Germany**

Dr Heidi Meyer updated the Committee on recent PEI standardization activities and associated developments. These had included participation in the revision of the WHO Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries, and in the NC3Rs review of animal testing in WHO guidelines – both of which would be discussed at the current meeting (see sections 3.1.1 and 3.1.2 respectively). Dr Meyer then summarized ongoing PEI involvement in the drafting of a number of WHO written standards, which included the WHO Guidelines to assure the quality, safety and efficacy of for live attenuated rotavirus vaccines (oral), the WHO Guidelines on procedures and data requirements for changes to approved vaccines, and the WHO addendum on the nonclinical and clinical evaluation of mAbs for use specifically against SARS-CoV-2.

With regard to WHO measurement standards, PEI had taken the lead in developing the WHO International Reference Reagent for antibodies to Ross River virus for neutralization assays (human, plasma) that would be proposed for establishment at the current meeting (see section 9.1.2 below). PEI had also participated in other collaborative studies, including on the Second WHO International Standard for SARS-CoV-2 RNA for NAT-based assays, which was also being proposed for establishment at the current meeting (see section 8.1.1 below). PEI had also provided support to the WHO prequalification programme for IVDs by regularly assessing dossiers and contributing to the Technical Specification Series for IVDs. The PEI BloodTrain programme had
provided support to the WHO Achilles programme and to WHO regulatory systems strengthening activities by organizing and supporting workshops and webinars. Dr Meyer concluded by informing meeting participants that PEI had been designated as an EU Reference Laboratory for high-risk IVDs, which would involve verifying IVD performance, undertaking batch testing and providing expert advice.

2.3 Cross-cutting activities of other WHO committees and groups

2.3.1 Feedback from the 56th and 57th meetings of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

Dr Luther Gwaza began by providing an overview of WHO activities in developing and establishing norms and standards for pharmaceuticals, and promoting their implementation in countries. Specific areas of work include the publication of the International Pharmacopoeia and WHO recommendations for pharmaceuticals, the provision of International Chemical Reference Substances, the implementation of an external quality assurance scheme, and the WHO Biowaiver Project. Dr Gwaza highlighted that the International Pharmacopoeia provided a valuable resource, particularly for countries lacking national quality control standards in this area. Dr Gwaza moved on to the issue of the international comparator products currently included in the WHO Model List of Essential Medicines (EML) to support the WHO prequalification of biotherapeutics and to increase access to biosimilar products. The list of international comparator products is a key resource for manufacturers and regulators, and is produced according to strict selection criteria for product inclusion. Feedback received during an informal consultation on biosimilars had included the suggestion that consideration be given to the inclusion of biosimilars on the list of international comparator products.

Dr Gwaza then summarized the main outcomes of the 56th ECSPP meeting, which had included the adoption of 10 texts on quality assurance and regulatory guidance, the approval of 17 specifications for active substances and specific dosage forms, the establishment of 11 new International Chemical Reference Substances, and approval of a general chapter for inclusion in the International Pharmacopoeia. Dr Gwaza highlighted the publication of the 10th edition of the WHO Quality Assurance of Pharmaceuticals Compendium, an important resource for assuring the quality, safety and effectiveness of medicines that now reflected the guidelines adopted at recent meetings of the ECSPP. In addition, a number of changes had been made in the 11th International Pharmacopoeia, published in 2022. Dr Gwaza also provided an overview of the guidelines and emerging topics discussed at the recent 57th meeting of ECSPP, which had been held in early October 2023. Dr Gwaza concluded by describing an online platform that had been introduced to facilitate the development of
WHO guidelines and other documents in this area. This platform allowed for the more systematic management of all steps of document development, including the collection and reviewing of feedback received from experts during public consultations.

Responding to the suggestion that biosimilars be included on the list of international comparator products, the Committee felt that such products were more complex than generic small molecules, and that existing WHO guidelines on biosimilars sufficiently addressed the challenges relating to the identification of comparator products for biotherapeutics. However, the Committee agreed to reflect on this suggestion between now and its next meeting. The Committee went on to emphasize the importance of working with ECSPP to ensure that all WHO guidance on good manufacturing practices is consistent.

2.3.2 Update from the Strategic Advisory Group of Experts on IVDs

Dr Ana Aceves Capri updated the Committee on the outcomes of the 4th SAGE IVD meeting held in November 2022, during which applications for the fourth WHO Model List of Essential In Vitro Diagnostics (EDL 4) had been reviewed. A total of 12 EDL applications had been made – 9 for new IVD test categories, two for edits to IVDs listed in EDL 3, and one so-called “do not do” recommendation. SAGE IVD also discussed the role of the EDL in increasing the availability, access and proper use of IVDs, and made several general recommendations with regard to the EDL process. These included streamlining and encouraging participation in the application process, and better understanding the needs of stakeholders through outreach efforts. Recommendations on the EDL strategy included increasing the visibility of the initiative, particularly at national level.

Activities moving forward would include: (a) the development of a methodology to count the IVD tests in the lists; (b) reviewing the structure of the EDL and harmonizing the assay formats used; (c) drafting a guide on the implementation of national EDLs; and (d) developing a subset of the IVDs listed in the EDL tailored to emergency situations, including those for use in interagency emergency health kits. Dr Aceves Capri concluded by listing the IVD tests currently under consideration for inclusion in EDL 5, and which would be reviewed at the next SAGE IVD in November 2024.

During discussion, Dr Aceves Capri clarified that inclusion of an IVD test in the EDL was not only based on its performance characteristics but also took into account its public health impact and cost effectiveness where the necessary data were available. The application process considers all tests and brands reviewed by the experts. However, SAGE IVD did not currently include standardization as a specific criterion, while there was also a recognized need to increase its expertise in the area of blood transfusion testing.
2.3.3 **Update from the Strategic Advisory Group of Experts on Immunization**

Dr Joachim Hombach outlined the discussions that had taken place during a meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization held in September 2023. Based on epidemiological and other evidence reviews, SAGE had now revised its good practice statement on the use of variant-containing COVID-19 vaccines and updated the WHO roadmap for prioritizing the use of such vaccines to account for recent developments. Available data suggest that monovalent Omicron XBB vaccines provide modestly enhanced protection compared with bivalent variant-containing vaccines and monovalent index virus vaccines. SAGE now recommends the use of a simplified single-dose regime for primary immunization with most COVID-19 vaccines to improve acceptance and uptake, while providing adequate protection to most people who have had at least one prior infection. Where monovalent XBB vaccines are unavailable, any WHO emergency use listed or prequalified bivalent variant-containing or monovalent index virus vaccines may be used to protect groups at high risk of severe disease. The updated roadmap for COVID-19 vaccination that was approved reflects this simplified schedule, the updated recommendations on revaccination and currently available COVID-19 vaccines.

In addition, SAGE also reviewed and discussed the efficacy and safety of the recently approved live attenuated dengue vaccine TAK-003. This vaccine is based on a DENV2 virus expressing E and prM proteins of all four dengue serotypes (DENV1–4) and provides high protection against DENV2 in seropositive and seronegative individuals, and moderate protection against the remaining serotypes in seropositive individuals. There was no evidence of protection of seronegative individuals against DENV3 and DENV4 and the available data were inconclusive regarding the safety of the vaccine. Although the potential safety risk is much smaller than for the current alternative vaccine, it remains biologically plausible and could only be assessed in a large post-implementation study. Dr Hombach summarized the current conditional WHO policy recommendations on the introduction and use of the TAK-003 dengue vaccine in routine immunization programmes, and associated supporting activities, and highlighted that these recommendations currently differ in for settings in which dengue poses a significant public health problem due to high transmission of the virus, compared to settings with only low to moderate dengue transmission.

Dr Hombach then outlined in detail the WHO recommendation on the programmatic use of vaccines (currently RTS,S/AS01 and R21/Matrix-M) for the prevention of *Plasmodium falciparum* malaria in children living in malaria-endemic areas. This recommendation had been based on a full evidence review of R21/Matrix-M conducted by SAGE and the Malaria Policy Advisory Group. Dr Hombach concluded by updating the Committee on recent developments
with regard to chikungunya vaccines, the most advanced of which is the live-attenuated vaccine VLA1553. A recent clinical study had met its primary end-point, reporting protective antibody titres in 98.5% of volunteers (95% CI = 96.2–99.6) 28 days after a single vaccine dose, which was significantly higher than in the placebo group.

Seeking clarification of the evidence underpinning the simplified COVID-19 vaccination regime, the Committee was informed that the updated recommendation had been based on immunogenicity data in populations that had been vaccinated and/or previously infected with SARS-CoV-2. The Committee also sought clarification of the apparent differences in the number of COVID-19 cases in different WHO regions, and was informed that this was largely attributable to differences in reporting. The Committee went on to discuss the conditional WHO policy recommendations on TAK-003 vaccine use. Noting that both Denvaxia and TAK-003 are approved in some countries in the WHO South-East Asia Region, the Committee was informed that in order to minimize the risk of vaccine-enhanced disease, SAGE was updating its position for each vaccine, and that although this risk had not been documented for TAK-003, it remained plausible. Asked about the use of dengue vaccines in the context of endemic disease seasonality, Dr Hombach emphasized that the conditional recommendations were based on epidemiological evidence, where the majority of people have had at least one infection. The recommendations aimed to minimize risk while leveraging the benefit of vaccination and advised that vaccine roll-outs should proceed with caution and the opportunity taken to gather more data. With regard to the assessment of chikungunya antibody titres, the Committee was assured that use of the current WHO international standard had been encouraged to harmonize data.

2.3.4 Update on the WHO Model Lists of Essential Medicines

Dr Benedikt Huttner began his update by noting that essential medicines are defined by WHO as those medicines that satisfy the priority health care needs of a population. The criteria for selecting medicines for the EML or EML for children (EMLc) were based on disease prevalence, public health relevance, evidence of clinical efficacy and safety, relative cost and cost-effectiveness. Since its inception in 1977, the number of medicines on the EML had more than doubled, with 85 applications for additions or changes to the list being reviewed at the 24th meeting of the WHO Expert Committee on Selection and Use of Essential Medicines in April 2023. Among the key decisions made several highly priced cancer medicines had not been recommended, while two medicines for the treatment of alcohol use disorder and a nicotine replacement therapy for smoking cessation were included on the core list of the EML. Dr Huttner went on to highlight the decisions made for EML inclusion or non-inclusion.
for a range of other biological products including a “polypill” for the prevention of atherosclerotic cardiovascular diseases, antimicrobials, and medicines for diseases of the nervous system, mental and behavioural disorders, Ebola virus disease and COVID-19.

With regard to medicines for the treatment of COVID-19, Dr Huttner acknowledged that compared to WHO living guidelines for COVID-19 therapeutics, the EML changed slowly – though the Expert Committee for the EML did recommend that effective and safe therapeutics for COVID-19 should be considered as essential medicines, and be prioritized by countries for national procurement. Listing of medicines in the EML for use in public health emergencies that would subsequently have to be removed as they were no longer relevant was a scenario that was to be avoided. In this regard, the Expert Committee for the EML had further recommended the addition of a new section to both the EML and EMLc that did not list specific medicines but instead referred national decision-makers to the WHO living guidelines.

Dr Huttner concluded by outlining the need for a revised procedure for updating the EML that could improve the quality and consistency of applications. Since the procedure was last updated in 2001, the medicines landscape had become increasingly complex. The current focus of the application process on single medicines made it difficult to obtain a broader sense of the situation, especially in areas without dedicated WHO technical teams or guidelines. Clarification of the role of the EML regarding innovative medicines and in public health emergencies was also required.

During discussion, the Committee enquired as to why CAR T cells for cancer therapy had not been included on the EML. Clarification was given that such sophisticated treatments pose significant challenges as they called for specialized centres and were likely to be unaffordable in most settings. Nevertheless, CAR T cell therapy would probably be added to the EML in due course, once the supporting data were sufficiently mature. Regarding the use of drug combinations in cancer therapy, it was suggested that the publication of treatment guidelines and clinical reviews based on multiple products would be helpful in supporting EML applications. Dr Huttner clarified that efforts were made to evaluate all available guidance and evidence when recommending the inclusion of a medicine on the EML.

2.3.5 Update from the 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. Such INN are used for prescribing in most countries. Remarking on trends in INN requests, Dr Balocco noted that in recent years, requests for biological products,
and mAbs in particular, had dominated, while there had also been a marked increase in cell-based INN requests since 2014. Dr Balocco then highlighted the online School of INN platform, which it is hoped will encourage the use of INN by all stakeholders as a common nomenclature for all pharmaceutical substances worldwide. Reviewing how the number of INN and stems had changed over time, Dr Balocco specifically highlighted the discontinuation of the stem -mab, as well as the list of INN for mRNA and protein vaccines against SARS-CoV-2, both of which had been discussed in detail at the 76th meeting of the Committee in October 2022.

Dr Balocco went on to outline the development of a WHO INN Open Database for Proteins (ODP) intended to consolidate information currently held in various file formats. This database will facilitate the assessment of INN requests and offer an internationally certified data source for registered proteins. The ODP will include a set of tools and be structured to provide easy access to data, including protein sequences, post-translational modifications and metadata. Good progress had been made in migrating MedNET documents into the ODP with 70% of these validated and available so far.

The Committee enquired how an mRNA expressing a protein would be handled in the ODP and clarification given that such requests would focus on the protein structure. Whereas traditional vaccines (such as inactivated or live attenuated vaccines) have not been assigned INN, novel vaccines with well-characterized active ingredients meet the criteria for INN assignment. Although the Committee acknowledged that naming each active ingredient of novel vaccines separately was logical, it also noted that it might be challenging to name multivalent influenza vaccines in a timely manner to avoid unduly complicating regulatory approval. The Committee was informed that the INN Expert Group was reflecting on this but currently remained undecided on the proposed nomenclature.
3. International Recommendations, Guidelines and other matters related to the manufacture, quality control and evaluation of biological products

3.1 Vaccines and related substances

3.1.1 Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries

Large-scale disease outbreaks can result in a severe disease burden, claiming millions of lives and causing economic hardship worldwide. The implementation of strategies to shorten the time between the emergence of a pathogen and the availability of safe and effective vaccines is crucial in strengthening global health security. Following the 2009 H1N1 influenza pandemic, poor regulatory preparedness was identified as a critical factor in delaying or preventing the use of pandemic influenza vaccines, especially in non-vaccine producing countries. Subsequently, at its meeting in October 2016, the ECBS had recommended the adoption of the WHO Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries. Since then, a number of disease outbreaks, including the COVID-19 pandemic, had highlighted the need to broaden the scope of WHO guidance in this area to include other vaccines used during pandemics and other public health emergencies.

The Committee was provided with an overview of the development and structure of the revised WHO Guidelines which had now been produced and were being presented to the Committee for its consideration. The revised Guidelines provided guidance to NRAs of importing countries on the regulatory oversight of pandemic or other emergency use vaccines, including authorization and post-authorization activities. The document emphasizes the role of regulatory reliance and the importance of risk-based decision-making in ensuring the approval and timely availability of life-saving vaccines during a pandemic or other public health emergency, with the principles set out potentially also being applicable to therapeutic and other medical products. Although primarily intended for NRAs, the revised guidance was also likely to be of interest to national immunization technical advisory groups, manufacturers and authorities responsible for planning and managing emergency vaccination programmes. The document had been subjected to two rounds of public consultation and had been well received. All suggestions and other feedback provided were assessed and the text amended where required.

Acknowledging the considerable efforts of the drafting group, the Committee welcomed the revised WHO Guidelines and highlighted the need to follow up its publication with implementation workshops, especially where NRA functioning was weak. Addressing concerns that important aspects of
pandemic influenza preparedness guidance might be lost as a consequence of
the replacement of the previous influenza-specific Guidelines, the Committee
was assured that other WHO pandemic influenza preparedness guidance would
be retained. The Committee concurred with the decision to entirely replace the
previous Guidelines but noted that in the longer term the potential development
of disease-specific addenda might provide one way of addressing issues unique
to individual diseases, while also cautioning against the duplication of the
existing guidance.

After further consideration and review of all the issues raised, the
Committee recommended that document WHO/BS/2023.2453 be adopted and
annexed to its report (Annex 2).

3.1.2 Review of animal testing requirements in WHO guidelines
and recommendations for biological products: implementing
the 3Rs principles

Animal testing approaches have long been used during the development of
biotherapeutics and vaccines to provide insights into their mechanisms of
action, and to evaluate their safety and efficacy. In addition, the same methods
continue to be used post-approval as part of lot release for the quality control and
lot release of many vaccines and biotherapeutics. However, animal-based assays
are inherently variable and highly time consuming, potentially causing delays in
the availability of life-saving products, while also placing a considerable burden
on the resources of manufacturers and NCLs. Globally, there is also a lack of
harmonization of animal testing requirements across regulatory jurisdictions.

In light of recent significant advances in the implementation of non-
animal technologies for the quality control of biological products, driven in part
by increasing awareness of the need for greater and more consistent application
of the 3Rs principles, WHO had commissioned an independent review of the
animal-based methods currently recommended in its written standards for
biological products. The purpose of this review had been to determine which
tests were currently recommended for product quality control and lot release,
and to identify opportunities for the inclusion of non-animal test methods or
other 3Rs strategies where scientifically justified. The review had also explored
the barriers to the adoption of 3Rs principles in quality control testing facing
NRAs, NCLs and manufacturers. Having now being completed, the final review
report and associated proposals were presented to the Committee.

Of the 81 active WHO written standards reviewed, 63 described
animal testing methods used to detect the presence of adventitious agents, or
to assess the neurovirulence, potency, pyrogenicity and toxicity of biological
products prior to market release. Each of these five areas had been reviewed by
a focus group of experts and revised language proposed to better incorporate
and encourage the use of 3Rs approaches, and to ensure greater consistency between different documents. Clarification was given that project stakeholders had been engaged through a series of regional workshops to ensure that their views and experiences were reflected in the report, with surveys conducted among manufacturers and NRAs highlighting their concerns regarding animal testing, and a desire to implement non-animal methods wherever applicable and scientifically justified. Nevertheless, despite a well-publicized decision by WHO to no longer recommend the use of the abnormal toxicity (also known as the general safety test), the survey had also revealed its continued use in some settings. Further proposals in the report included: (a) development of general WHO guidance and statements on the implementation of 3Rs practices into lot-release activities; (b) drafting of a WHO manual specifically on the adoption of 3Rs approaches during pyrogenicity and endotoxin testing; and (c) identifying opportunities to improve the accessibility and utility of WHO guidance documents going forwards.

The Committee expressed its thanks to NC3Rs for its considerable efforts and commitment to the project. Acknowledging both the quality and comprehensiveness of the work undertaken during the review process, the Committee also commended the final report, remarking on its clear presentation, attention to detail and the considerable input of acknowledged experts. The Committee recommended that a working group be established to build upon the findings of the report and to help develop further WHO guidance in this area. The consensus view of the Committee was that WHO should develop science-based guidance encouraging the replacement of animal tests with non-animal tests in the quality control of vaccines and other biological products, where applicable and scientifically justified. In addition, while noting that resources are required for revising WHO written standards, the Committee felt that the revised language of the texts proposed in the report was important and should be incorporated wherever possible into respective WHO guidance. It was noted that promoting and facilitating access to an associated NC3Rs database highlighted in the report could provide users with advanced access to the proposed texts ahead of the likely more gradual revision of the WHO written standards themselves.

Concern was expressed that despite more than 80% of manufacturers and NRAs being aware of the WHO decision to remove the abnormal toxicity test/general safety test, 69% of NRAs still accepted data from such tests. As implementation of this decision in a particular jurisdiction rests with the NRA, the Committee suggested that ways be found to encourage NRAs to stop requiring the test. This might include making explicit mention of the WHO decision in the introductory text of Annex 1 of the reports of the Committee, which appears each year in the WHO Technical Report Series. In addition, WHO might also consider publishing a clear and unambiguous statement on the recommended discontinuation of the test on relevant parts of the WHO website.
4. International reference materials – biotherapeutics other than blood products

All reference materials established at the meeting are listed in Annex 3.

4.1 WHO international reference standards for biotherapeutics other than blood products

4.1.1 Fourth WHO International Standard for thyroid-stimulating hormone (human, pituitary)

The measurement of thyroid-stimulating hormone (TSH) by immunoassay is important in the diagnosis and management of thyroid disorders, with the level of TSH in patient serum typically reported in milli-International Units per litre (mIU/L). The first WHO reference standard used to standardize pituitary TSH immunoassays was established in 1974. Following concerns regarding the commutability of the current Third WHO International Standard for thyroid-stimulating hormone and its predecessors, and the potential impact of this issue on the harmonization of TSH measurements between methods and laboratories, the International Federation of Clinical Chemistry and Laboratory Medicine had established a Committee for the Standardization of Thyroid Function Tests (C-STFT). In order to facilitate the comparison of assay methods, a C-STFT reference panel of serum samples had subsequently been developed for use in combination with the WHO reference standard.

Both the current WHO international standard and C-STFT serum panel were now almost depleted and needed to be replaced. A candidate material (NIBSC code 81/615), prepared in the early 1980s from the same batch of pituitary extract used for the previous WHO international standards, had been evaluated in an international collaborative study involving 17 laboratories in eight countries. Despite having been assigned a value in previous collaborative studies, it was considered important to reconfirm the unitage of the candidate material relative to the current WHO international standard, and to assess its suitability to serve as a WHO international standard for current TSH immunoassay methods. Fifteen laboratories, each performing a different immunoassay, provided the data used for value assignment and commutability assessment, with two further laboratories providing the data used for stability assessment. Analysis of the candidate material 81/615 relative to the current WHO international standard produced linear and parallel dose-response relationships in all laboratories. Following the exclusion of data from two laboratories from the statistical analysis due to outlier results, a geometric mean potency of 11.7 mIU/ampoule was calculated, with an inter-laboratory geometric coefficient of variation (GCV) of 4.5% (n = 13). Analysis of the current WHO international standard and
candidate material 81/615 alongside the C-STFT serum panel confirmed their poor commutability, with the impact of this to be mitigated by use of the panel to harmonize TSH measurements.

Analysis of data from an accelerated thermal degradation study of the candidate material 81/615 predicted an annual loss of potency of 0.03–0.18% when stored at −20 °C, which is similar to the stability predicted for the current WHO international standard. Taken together with real-time data for TSH standards produced from similar material, this finding indicated that the candidate material would be stable when stored at −20 °C.

Discussion focused on the commutability problems associated with this international standard. Although MHRA had considered the use of a different source material to address this issue, the quantity of serum required presents a challenge, especially as potential donors are usually treated. Noting that different types of immunoassays had been used in the collaborative study, the Committee was informed that there was no clear pattern in the lack of commutability between different methods that might inform the choice of future replacement materials. Although users were largely aware of the commutability issue, it remained important to get this message across accurately in the instructions for use and elsewhere. The WHO standard will continue to be needed as the C-STFT serum panel was calibrated in mIU but it may in future increasingly be used as a run control. The Committee was satisfied that any loss of activity of the current standard, used in the collaborative study, would have been very small and therefore unlikely to result in unitage drift or to impact upon clinical decision-making.

The Committee considered the report of the study (WHO/BS/2023.2454) and recommended that candidate material 81/615 be established as the Fourth WHO International Standard for thyroid-stimulating hormone (human, pituitary) with an assigned unitage of 11.7 mIU/ampoule.

4.1.2 Second WHO International Standard for alpha-fetoprotein (human)

The measurement of alpha-fetoprotein (AFP) in human serum is used to monitor diseases such as chronic active hepatitis and hepatocellular carcinoma, as well as birth defects such as anencephaly, omphalocele and spina bifida. A range of commercial immunoassays are available, including automated and ELISA platforms, with most being traceable to the current WHO international standard established in 1975. As stocks of this standard had now been exhausted, a replacement WHO international standard was urgently required.

A candidate material (NIBSC code 22/216) consisting of highly purified AFP from human cord serum diluted in human serum, had been filled and freeze-dried in ampoules as a prospective replacement. The suitability of the material to serve as a WHO international standard had been assessed, alongside the current
WHO international standard and a panel of serum samples, in an international collaborative study involving nine laboratories in four countries. The resulting data, obtained using a broad range of clinical AFP immunoassays, indicated that the prospective replacement standard behaved in a similar manner to the current international standard, and was used to assign a value relative to it. Further analysis of the immunoassay results using a calibration effectiveness approach suggested that for at least some methods the candidate material was commutable with patient samples. Overall, there was an improvement in harmonization between laboratories and methods at higher AFP concentrations when reported relative to the candidate material but poorer harmonization at lower AFP concentrations. As the study was not able to assess the impact of experimental variation on commutability, manufacturers would be recommended to carry out their own assessment of the behaviour of the candidate material 22/216 in their assays compared to native samples, particularly where the laboratory methods tended to be non-commutable at lower concentrations. An accelerated thermal degradation study had demonstrated that the candidate material was stable, with a predicted degradation rate of 0.07% per year when stored at −20 °C.

The Committee viewed this to be a straightforward replacement and having considered the report of the study (WHO/BS/2023.2461) recommended that candidate material 22/216 be established as the Second WHO International Standard for alpha-fetoprotein (human) with an assigned unitage of 7800 IU/ampoule.

4.1.3 Sixth WHO International Standard for follicle-stimulating hormone and luteinizing hormone for bioassay (human, urinary)

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are glycoprotein hormones important in the regulation of follicular growth, pubertal maturation and reproductive processes. Human urinary FSH and LH are widely used therapeutically to treat infertility, as well as to control ovarian hyperstimulation in assisted reproductive technologies. The potency of FSH/LH products is determined using an in vivo bioassay calibrated in IU. A WHO international standard for human urinary FSH/LH has been available since the 1960s and stocks of the current fifth international standard are now almost depleted.

A candidate material (NIBSC code 21/344) had been produced from a preparation of highly purified human urinary FSH/LH and formulated to be similar to the current WHO international standard. An international collaborative study involving six laboratories in six countries had been conducted to assess the suitability of candidate material 21/344 as a replacement WHO international standard. Each laboratory performed in vivo bioassays to assign a potency to the material relative to the current WHO international standard using a parallel-
lines model. A total of 34 assays had been performed for FSH and 32 for LH. The overall geometric means for FSH and LH content of the candidate material were 177 IU/ampoule and 170 IU/ampoule respectively. The data demonstrated good agreement between laboratories, with a GCV of 8% obtained for FSH assays and 4% for LH assays. There was no significant loss of FSH or LH activity in ampoules stored at elevated temperatures for 7 months which, taken together with the good stability record of previous such standards of similar formulation, indicates that the material would be stable under long-term storage at −20°C.

Reflecting on its earlier discussion on the replacement of animal-based tests (see section 3.1.2 above), the Committee questioned the continued use of in vivo assays to assess the potency of FSH/LH products. Clarification was given that at present there was no suitable alternative to such assays. Although it is possible to measure the biological activities of FSH/LH preparations in vitro, it is recognized that the in vivo and in vitro assays measure different biological processes. The biological activity assessed in vivo depends on the extent of glycosylation of the FSH or LH molecule which governs its circulating half-life, whereas the biological activity measured in vitro depends on the binding of FSH or LH to its receptor expressed in a cell line. As any manufacturing process-dependent changes to, or differences in, the glycosylation of the FSH or LH molecule can affect each of the assays differently, any international standard (which will likely have a different glycosylation pattern to an FSH/LH product sample) must be value assigned using the in vivo bioassay to maintain traceability to the IU. However, for any particular FSH/LH preparation, it is possible to derive a correlation between the biological activities assessed in vivo and in vitro. As a result, manufacturers can, in line with the 3Rs principles, use an in vitro assay for routine in-house quality control and lot-release purposes.

The Committee considered the report of the study (WHO/BS/2023.2462) and recommended that candidate material 21/344 be established as the Sixth WHO International Standard for follicle-stimulating hormone and luteinizing hormone for bioassay (human, urinary) with assigned unitages of 177 IU/ampoule (FSH) and 170 IU/ampoule (LH).
5. International reference materials – blood products and related substances

All reference materials established at the meeting are listed in Annex 3.

5.1 WHO international reference standards for blood products and related substances

5.1.1 First WHO International Standard for thrombin activatable fibrinolysis inhibitor (plasma)

Thrombin activatable fibrinolysis inhibitor (TAFI), also known as procarboxypeptidase U or CPB2 gene product, is a protein that plays a crucial role in regulating fibrinolysis. Synthesized and secreted predominantly by the liver, TAFI circulates in the bloodstream as an inactive zymogen. TAFI can be activated to form TAFIa by the enzymes thrombin and plasmin, resulting in cleavage of C-terminal lysines from partially degraded fibrin by TAFIa, thereby inhibiting fibrinolysis and promoting clot stability. The dysregulation of TAFI/TAFIa has been linked to various pathological conditions, including thrombosis and inflammatory disease. Measurement of TAFI levels or activity in blood may therefore be important for the diagnosis, prognosis and monitoring of these conditions. Due in part due to differences in the calibrators and methodologies used, the results obtained when investigating TAFI as a disease marker are confusing and often contradictory, with wide variations observed in the estimates of plasma TAFI concentration. Therefore, a common reference material for TAFI for use by manufacturers of commercial kits and by academic/clinical laboratories was required to harmonize global measurements.

A candidate material (NIBSC code 17/200) consisting of normal pooled plasma provided by the National Blood Service in the United Kingdom had been lyophilized and sealed in 5 mL glass ampoules. An international collaborative study involving 10 laboratories in seven countries had then been conducted to assign global consensus mean values for TAFI antigen and total potential TAFIa activity (hereafter referred to simply as TAFI activity) to normal pooled plasma, with the TAFI antigen expressed in both IU and SI units (µg) and TAFI activity expressed in IU. Using routine assay methodologies as far as possible, participant laboratories measured the TAFI antigen and/or TAFI activity of the candidate material 17/200, a locally collected normal plasma pool and three control plasma samples representing normal, low and high TAFI levels. Study results indicated that the candidate material 17/200 performed well in all assays of the control samples, with the data supporting the establishment of a WHO international standard to improve the global harmonization of both TAFI antigen and TAFI activity measurement, with assigned unitages of 0.92 IU/ampoule and 0.87 IU/ampoule respectively.
Although many commercial calibrators for TAFI antigen currently have assigned values in SI units (µg/ml), consensus mean values for SI units are not acceptable for primary standards. A robust method for the quantitation of TAFI in plasma by isotope dilution tandem mass spectrometry was therefore developed and performed at MHRA. Based on the results obtained, it was proposed that the WHO international standard also be assigned an SI value for TAFI antigen of 7.43 µg/ampoule. A variance components analysis was also performed to calculate the intra-assay and inter-assay components of uncertainty in order to determine the standard uncertainty for the proposed unitage (7.05–7.82 µg/ampoule).

Accelerated degradation studies were conducted using samples stored at elevated temperatures for 4 months and for 1 year, with no significant loss of potency observed at 20 °C for 1 year, indicating good stability of the TAFI antigen. TAFI activity also exhibited very good stability when assessed after 1 year at 20 °C and at 37 °C, with data predicting a loss of 0.096% per year at −20 °C. Stability following reconstitution was also monitored for 6 hours with no measurable loss of TAFI antigen or activity measurements.

The Committee was informed that the results of the collaborative study had been reviewed by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (SSC/ISTH), which noted that the study had been well conducted, and expressed its agreement with the proposed value assignments. With regard to the assignment of both an SI unit and an absolute value in µg/ampoule to the TAFI antigen component, the Committee noted that tools such as mass spectrometry were increasingly allowing for the measurement and quantification of such antigens and congratulated MHRA on the absolute assignment made.

Having taken note of the comments made by the SSC/ISTH, the Committee considered the report of the study (WHO/BS/2023.2457) and recommended that candidate material 17/200 be established as the First WHO International Standard for thrombin activatable fibrinolysis inhibitor (plasma) with assigned values of: (a) 0.87 IU/ampoule for TAFI activity; and (b) 0.92 IU/ampoule and 7.43 µg/ampoule (expanded uncertainty limits = 7.05–7.82 µg/ampoule) for TAFI antigen.

5.2 Proposed new projects and updates – blood products and related products

5.2.1 Proposed Seventh WHO International Standard for blood coagulation factor VIII and von Willebrand factor (plasma)

The WHO international standard for blood coagulation factor VIII (FVIII) is required for the assignment of FVIII potency to virus inactivated fresh frozen plasma (VIFFP) products. The international standard is also required for the
harmonization of laboratory assays used for the diagnosis and monitoring of patients with FVIII deficiency and von Willebrand disease, and is thus used by manufacturers of plasma calibrators, diagnostic and clinical laboratories, plasma purification sites and manufacturers of VIFFP products.

The current WHO international standard for FVIII and von Willbrand factor (VWF) was established in 2009 with assigned IU for FVIII:C, FVIII:antigen, VWF:antigen, VWF:ristocetin cofactor and VWF:collagen binding (and subsequently for VWF:propeptide), with assigned “units” for VWF:GPIbR and VWF:GPIbM being added in 2018. With more than 1000 ampoules shipped each year, stocks deplete rapidly, and there was now a need to initiate replacement of the current sixth international standard. It was intended that all eight analytes would be assigned unitages relative to the current international standard in an international collaborative study, including assignment of IU for VWF:GPIbR and VWF:GPIbM. Normal plasma pools sourced from the National Blood Service in the United Kingdom would be evaluated by 20–30 laboratories – though smaller numbers were expected to participate for the less commonly performed tests and/or where participant laboratory recruitment was likely to be more difficult (for example in the case of VWF:propeptide). It was anticipated that the collaborative study outcomes would be submitted for consideration by the Committee in 2025.

The Committee endorsed the proposal (WHO/BS/2023.2464) to develop a Seventh WHO International Standard for blood coagulation factor VIII and von Willebrand factor (plasma).

5.2.2 Proposed First WHO International Standard for quantitation of plasma anti-D levels

Alloimmunization with anti-D occurs as the result of transfusing rhesus D (RhD)-positive blood into RhD-negative recipients, or following the exposure of maternal RhD-negative blood to fetal RhD-positive blood. Such alloimmunization can lead to severe haemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies. The prevention of RhD alloimmunization by Rho(D) immunoglobulin is important in reducing the incidence of HDFN, with anti-D levels monitored throughout immunized pregnancies and clinical decisions made based on assay results.

Various methods are used for plasma anti-D quantitation, with continuous flow analysis by an autoanalyser for haemagglutination being the main method used in the United Kingdom, Ireland and France. Methods used in other countries include antibody titration by tube or column, as well as flow cytometric quantification. The use of non-standardized methods was historically associated with inter-laboratory variabilities of up to ± 100% of the mean. In the United Kingdom, a British Standard for anti-D for routine use in automated assay
techniques was developed and CE marked in 2005 under Directive 98/78/EC on in vitro diagnostic medical devices. The introduction of this and subsequent replacement batches, along with the use of standardized protocols, resulted in a significant reduction in interlaboratory variability to around 20%.

There was now an opportunity to repurpose the current British Standard (NIBSC code 73/517) by redefining it as a WHO international standard that would support the standardization of plasma anti-D quantitation by serological methods and improve harmonization across laboratories worldwide. The current British Standard 73/517 had been prepared from pooled citrated plasma containing anti-D from donors in the early, mid, and late stages of immunization, and previously evaluated for autoanalyser use by five clinical laboratories in the United Kingdom, with an assigned a potency of 11.5 IU/ampoule for anti-D (Rho) antibodies. In 2019, three transfusion centres assessed the stability of anti-D in 73/517 and found no loss in potency, indicating sufficiently stability for at least another 10 years.

British Standard 73/517 would be reassessed for use as a candidate WHO international standard in an international collaborative study. As the preparation was specifically intended for use in automated haemagglutination assays, the standard may not be suitable for all other methods. In any case, potency would be assigned either in IU or titre levels for plasma anti-D to allow for improved global harmonization. As flow cytometry is also used globally, the collaborative study would also validate and confirm the potency for use in this method. It was anticipated that the collaborative study outcomes would be submitted for consideration by the Committee in 2025.

The Committee commented that it would be important to ensure that different RhD genotype/phenotypes and D variants were included in the collaborative study. It was also noted that many laboratories worldwide continued to use the tube-based assay, especially in prenatal populations to predict the risk of HDFN, while flow cytometry was mainly used during pregnancy and postpartum to estimate the amount of fetomaternal haemorrhage. Such differences in the test methods used and their distinct clinical purposes should also be reflected in the collaborative study.

The Committee endorsed the proposal (WHO/BS/2023.2464) to reassess British Standard 73/517 for use in the relevant methods and to establish it as a First WHO International Standard for quantitation of plasma anti-D levels.

5.2.3 Proposed Third WHO International Standard for protein C (plasma)
Protein C is a vitamin K-dependent coagulation inhibitor which acts on FV and FVIII in the presence of protein S and phospholipids. The WHO international standard for protein C has two associated analytes – functional and antigen – and is required to: (a) assign calibrator potency during laboratory diagnosis
of protein C deficiency in patients as part of thrombophilia screening should they present with thrombosis; and (b) for the value assignment of functional protein C to therapeutic products including VIFFP products. Although sufficient stocks remain for more than 3 years, the current WHO international standard is now almost 20 years old and a new standard is required following advances in measurement and other technologies in the field. The envisaged rate of use of the proposed replacement standard by diagnostics and therapeutics manufacturers is around 300 ampoules per year which based on a proposed batch size of 6000 ampoules should last for around 20 years.

Using human plasma sourced from the National Blood Service in the United Kingdom, a multicentre collaborative study involving 20–30 laboratories would be conducted to assign values to both the functional and antigen analytes of the standard. Stability would be continuously monitored, with data from the current standard indicating stability for ambient shipment and no loss of activity to date when stored at −20 °C. It was anticipated that the collaborative study outcomes would be submitted for consideration by the Committee in 2025.

In the absence of further comments, the Committee endorsed the proposal (WHO/BS/2023.2464) to develop a Third WHO International Standard for protein C (plasma).

### 5.2.4 Proposed Sixth WHO International Standard for thromboplastin (human, recombinant, plain)

International standards for thromboplastins are required to determine the International Sensitivity Index (ISI) of secondary standards and commercial thromboplastin test reagents used for the one-stage prothrombin time (PT) assay used to monitor patients undergoing treatment with vitamin K antagonists. The PT (measured in seconds) depends upon the thromboplastin reagent used and the technique employed in the device, and must be transformed into the International Normalized Ratio (INR) using a mathematical formula based on the ISI of the thromboplastin reagent and the Mean Normal Prothrombin Time to ensure equivalence between the various reagents and techniques. Stocks of the current WHO international standard for human thromboplastin (NIBSC code RTF/16) are now almost depleted and a replacement international standard needed. A commercial human recombinant thromboplastin preparation had now been identified as a potential source material and assessed in a trial fill.

In order to develop a harmonized reference measurement procedure based on the WHO manual tilt tube (MTT) method and to establish a complete reference measurement system for global standardization of the PT/INR test, a working group of stakeholders had been formed under the auspices of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the SSC/ISTH. The working group comprises representatives of calibration
laboratories, SSC/ISTH, MHRA, external quality assessment organizations, and manufacturers of reference materials and measurement procedures. Other objectives of the working group include establishing a network of at least three calibration laboratories running the harmonized MTT method for certifying the calibration of commercial thromboplastins from IVD manufacturers, and supporting the establishment of a single WHO international standard for thromboplastin to replace the current two co-existing WHO international standards for human and rabbit thromboplastins (NIBSC codes rFT/16 and RBT/16 respectively).

Based on the recommendations of the working group, a collaborative study involving four laboratories was being proposed to assign an ISI value to the potential source material relative to the current WHO international standard for human thromboplastin (RTF/16) using the harmonized MTT method. The use of the harmonized method would reduce the number of laboratories that had previously been required in the absence of method harmonization. In addition, although the 2013 WHO Guidelines for thromboplastins and plasma used to control oral anticoagulant therapy with vitamin K antagonists state that any collaborative study should test all relevant WHO international reference panels and other WHO reference standards (with the ISI assigned to the replacement standard being the mean of all values obtained), the working group had concluded that ISI value assignment for any given thromboplastin would be more precise if performed against a reference standard of similar composition and from the same species. As a result, value assignment will only be performed relative to RTF/16 and not to the current WHO international standard for rabbit brain thromboplastin (RBT/16). It was anticipated that the collaborative study outcomes would be submitted for consideration by the Committee in 2024.

Noting the recommendations made by the IFCC and SSC/ISTH working group, including the potential need to revise the 2013 WHO Guidelines, the Committee endorsed the proposal (WHO/BS/2023.2464) to develop a Sixth WHO International Standard for thromboplastin (human, recombinant, plain).

All reference materials established at the meeting are listed in Annex 3.

6.1 WHO international reference standards for in vitro diagnostics

6.1.1 WHO International Reference Reagent for antibodies to Q fever (Coxiella burnetii) antigens (plasma)

Query fever (Q fever) is a highly infectious zoonotic disease caused by the obligate intracellular pathogen *Coxiella burnetii*, which is usually transmitted to humans through inhalation of a spore-like small-cell variant or exposure to secretions from infected animals. *C. burnetii* typically causes a respiratory infection with mild influenza-like symptoms but more severe symptoms can include pneumonia and hepatitis. A small proportion of infected individuals develop chronic Q fever, which often results in endocarditis and is usually fatal if untreated.

Diagnosis of Q fever is normally confirmed serologically. The bacterium has two distinct antigenic phases with antibodies to phase II antigens developing early in infection and antibodies to phase I antigens predominating if the organism persists longer, making it possible to distinguish acute from chronic infections. In addition, although a Q fever vaccine is available, severe local reactions in those with pre-existing immunity make pre-vaccination screening essential, while also highlighting the need for an improved Q fever vaccine for use in post-exposure populations. Currently used serological assays include the immunofluorescence assay (IFA), ELISA and complement fixation assay, but there are currently no reference standards to facilitate the comparison of such methods or to assess assay inter-laboratory variations. In 2019, the Committee had endorsed a proposal to develop a WHO reference reagent for phase I and II antibodies to *C. burnetii*.

A candidate material (NIBSC code 21/304) consisting of a pool of human plasma donations from individuals with Q fever was filled and lyophilized in ampoules, and had now been evaluated in an international collaborative study involving seven laboratories in four countries. Study results indicated that candidate material 21/304 reduced the inter-laboratory variability of Q fever antibody measurements, and that this effect was more pronounced for IFAs compared with ELISAs, for which inter-laboratory variation was already low. Limited data obtained from both accelerated thermal degradation studies and in-use stability studies over a period of 3 months did not allow for the stability of the candidate material to be predicted. However, stability data for the ELISA phase II assay indicated only limited loss of potency. Stability monitoring would continue where possible, and additional analysis carried out to compare the 4 °C and the 37 °C samples with the −20 °C sample for both IFAs and ELISAs.
Reflecting on the high level of variability in the data returned by collaborative study participants, the Committee agreed that this was probably attributable to the widespread use of in-house assays and reagents, and to the known subjectivity associated with interpreting IFA results. The Committee was surprised to see the continued use of the complement fixation assay in this context but was informed that this was now rare.

The Committee considered the report of the study (WHO/BS/2023.2456) and recommended that candidate material 21/304 be established as the WHO International Reference Reagent for antibodies to Q fever (*Coxiella burnetii*) antigens (plasma) with assigned unitages of 100 U/ampoule for phase I immunoglobulin G and 16 U/ampoule for phase II immunoglobulin G.

### 6.1.2 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 WHO international standard are functional activity, free antigen and total antigen. The primary uses of the international 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 VIFFP and some prothrombin complex concentrates. Following steady demand, stocks of the Second WHO International Standard for protein S (plasma), established in 2006, were now depleted. In 2022, the Committee had endorsed a proposal to develop a replacement WHO international standard.

A candidate material (NIBSC code 22/202) consisting of a pool of 30 platelet-poor normal plasma provided by the National Blood and Transfusion Service in the United Kingdom had been freeze-dried in ampoules. An international collaborative study had then been conducted involving 21 laboratories in eight countries performing both functional and antigen assays. Laboratories also included locally sourced normal pooled plasma samples to assess the relationship between the IU and the normal plasma unit. The resulting data showed that, when assayed against the current international standard, intra-laboratory variability was low, with observed GCV of 0.6–13.5%, 0.2–16.8% and 1.3–14.1% for the functional activity, free antigen and total antigen assays respectively. For candidate material 22/20, similarly good agreement was also observed. Calculated as unweighted geometric means of laboratory means for each assay type, the overall mean potency estimates for the functional activity, free antigen and total antigen of candidate material 22/202 were 0.71, 0.83 and 0.88 IU/ampoule respectively. Although data from normal plasma pools were not used to assign unitages to the replacement standard, normal pool values provided by some participants were close to 1 IU/mL, indicating that each assay type was performing appropriately. The results of a 6-month accelerated thermal
degradation study, using a functional assay, predicted a loss of potency of 0.013% per year for the candidate material when stored at −20 °C.

Despite more than 100 major users of the standard being invited, both the Committee and collaborative study participants had expressed disappointment in the relatively small number of laboratories taking part, with only 10 datasets used to assign a total protein S value. While acknowledging that the costs associated with testing would have been prohibitive for some laboratories, the Committee discussed several potential approaches to improving future recruitment levels, including the use of contacts within WHO regional offices, WHO collaborating centres and the Committee itself. Noting that the Grubbs’ Test had been used to identify data outliers in the current study, the Committee went on to discuss more generally the statistical basis for excluding outliers from collaborative study analyses, which were currently decided on a case-by-case basis. The Committee advised that a standardized statistical approach to outlier detection be used when assigning units to a WHO international standard and suggested further discussion of this issue at a future meeting.

The Committee considered the report of the study (WHO/BS/2023.2460) and recommended that candidate material 22/202 be established as the Third WHO International Standard for protein S (plasma) with assigned unitages of 0.71 IU/ampoule for functional activity, 0.83 IU/ampoule for free antigen and 0.88 IU/ampoule for total antigen.

6.2 Proposed new projects and updates – in vitro diagnostics

6.2.1 Proposed First WHO International Standard for antibodies to hepatitis E virus; and First WHO International Reference Panel for antibodies to hepatitis E virus

With an estimated 20 million infections worldwide each year, hepatitis E virus (HEV) is of global health significance but clinically underdiagnosed. Although most HEV infections are asymptomatic and typically resolve within weeks, an estimated 3 million cases each year develop into acute hepatitis and result in more than 3% of all deaths due to viral hepatitis. HEV can be transmitted by the faecal-oral route, primarily through contaminated water or food products, and is common in LMIC with limited access to clean water, sanitation, hygiene and health services. Of the four viral genotypes that infect humans, types 1 and 2 are human viruses transmitted in contaminated water, with types 3 and 4 primarily found in animals and causing zoonotic infection due to consumption of undercooked meat. HEV can also be transmitted vertically from infected pregnant women, resulting in perinatal mortality and fetal loss. Laboratory diagnosis of HEV infection is based on various commercial serological assays detecting immunoglobulin M (acute infection) and immunoglobulin G but such
diagnosis is presently hampered by a lack of consistent reporting and poor inter-assay concordance.

Stocks of the current WHO International Reference Reagent for antibodies to hepatitis E virus were now depleted and the development of a First WHO international standard was being proposed as a replacement reference standard. In addition, in 2015, the Committee had endorsed a proposal to develop a WHO international reference panel for HEV antibodies and it was further proposed that this would also now be prepared. Sera sourced from laboratory-confirmed HEV cases would be evaluated in an international collaborative study as either potential reference panel members or for use as the international standard. Candidate sera for the international standard may also be sourced from individuals receiving the HEV vaccine Hecolin during a clinical trial in Pakistan. It was anticipated that the collaborative study would involve 10–20 laboratories, with the study outcomes being submitted for consideration by the Committee either in 2025 or 2026.

Noting the differences in the prevalence of genotypes between countries, the Committee advised that care be taken when selecting the individual sera to be pooled during development of the prospective international standard. In addition, although less common, every effort should be made to source type 2 sera. The Committee then endorsed the proposal (WHO/BS/2023.2464) to develop a First WHO International Standard for antibodies to hepatitis E virus, along with a First WHO International Reference Panel for antibodies to hepatitis E virus.

6.2.2 Proposed discontinuation of the First WHO International Standard for human C-reactive protein

C-reactive protein is a pentameric protein found in plasma and is a biomarker for acute inflammation caused by infection or inflammatory disease, and for cardiovascular and other diseases. It is synthesized in the liver in response to interleukin-6 released by macrophages and T cells and binds to dead cells and some types of bacteria to activate complement. The First WHO International Standard for human C-reactive protein (NIBSC code 85/506) was established in 1986 as a calibrator for use immunoassays. Although activity was assigned in mIU this was not widely adopted, with diagnostic measurements generally being reported in mg/L and users referring to the nominal content in µg quoted in the instructions for use. There are also several alternative certified reference materials available, including ERM-DA474 from the Joint Research Centre which is the calibrator used in the majority of assays and is traceable to the WHO international standard, as well as various reference materials from the Joint Committee for Traceability in Laboratory Medicine that can be obtained through national metrology institutes. As laboratories are increasingly using
amino acid analysis based on mass spectroscopy to quantify C-reactive protein, there will inevitably be a decline in demand for reference materials calibrated in activity units.

It was therefore being proposed that the First WHO International Standard for human C-reactive protein be discontinued once stocks became exhausted in approximately 3 years. In the meantime, the custodian laboratory (MHRA) will support the Joint Research Centre in establishing a replacement for its reference material by providing ampoules of 85/506. After reviewing the rationale for the proposed discontinuation of the WHO international standard, the Committee advised that the opinion of other interested parties be sought prior to the Committee making its recommendation at its meeting in October 2024.

All reference materials established at the meeting are listed in Annex 3.

7.1 WHO international reference standards for use in high-throughput sequencing technologies

7.1.1 WHO International Reference Reagent for gut microbiome DNA extraction (whole cell)

Changes in the human gut microbiome leading to its disturbance (dysbiosis) have been associated with a very broad range of diseases and disorders. Consequently, there is considerable and growing interest in the potential of microbiome-based medicinal products. Relatively recent developments in high-throughput sequencing (HTS) technologies and associated bioinformatics provide a wealth of approaches that can be used to survey the composition of the microbiome and investigate its association with different pathophysiological conditions. However, the range of such approaches presents challenges in ensuring the reproducibility and comparability of microbiome studies, with contradictory results obtained by similar studies. Such challenges will potentially hamper the development of innovative microbiome-based therapies, with the research community recognizing the importance of effective standardization in this area. At its meeting in April 2022, the Committee had recommended the establishment of two WHO international reference reagents to standardize the performance of microbiome sequencing and analytical pipelines. At the current meeting, the Committee was presented with the results of a further collaborative study to evaluate a candidate reference reagent for standardizing the performance of DNA extraction methods during studies of the gut microbiome.

The candidate material (NIBSC code 22/210) consisted of an equal ratio mix of 20 inactivated bacterial strains known to colonize the human gut, lyophilized in ampoules. The strains were well characterized, with their genome sequences publicly available through the National Center for Biotechnology Information. Care was taken to ensure that the bacteria were harvested in vegetative growth and that the candidate material did not contain bacterial spores. Early timepoints from an accelerated thermal degradation study indicated that the candidate material was stable over a range of temperatures based on metagenomic analysis, cell number and DNA concentration.

An international collaborative study involving 22 laboratories in 14 countries had been conducted to assess the suitability of candidate material 22/210 for use as a WHO international reference reagent, and to establish minimum quality criteria for users. Based on measures of DNA quantification,
purity and integrity, as well as species composition, use of the candidate material revealed a high level of variability between the different DNA extraction methods used. Notably, it was demonstrated that none of the methods used extracted DNA from *Alistipes finegoldii*, with many laboratories also failing to extract DNA from *Clostridium butyricum*. Statistical analysis of four key reporting measures for data generated by HTS (sensitivity, false-positive relative abundance, diversity and similarity) was conducted to establish minimum quality criteria for evaluating the relative efficiency of methods in extracting DNA equally from the different bacteria. Conversely, the study results indicated that DNA yield, purity and integrity were not reliable measures of whether a particular extraction method could accurately reconstruct the species composition. It was concluded that when used in conjunction with one of the previously established WHO international reference reagents (Gut-DNA-Mix coded 20/302), the candidate material 22/210 could be used to identify bias at different steps in the analysis of the gut microbiome by HTS, while also highlighting limitations such as method variability in extracting DNA from Gram-positive and Gram-negative bacteria.

The Committee enquired as to whether the species composition of the candidate material reagent was representative of current therapeutic developments. Clarification was given that the prospective international reference reagent consisted of the bacterial strains most commonly found in donor stools, and that its principal purpose would be to assess the performance of DNA extraction. The Committee went on to discuss possible reasons for the observed differences in the extraction of DNA from Gram-positive and Gram-negative species. While noting that some methods targeted different types of bacteria, and may therefore be biased regarding cell wall type, the Committee accepted that the reasons currently remained unclear but recognized that the issue was a common concern in the microbiome field. The Committee also noted that the minimum quality criteria would need to be revised as DNA extraction methods continued to develop, and as the complexity of the panel of strains increased. Regarding the impact of differences in genome size among the current panel members, the Committee was reminded that although genome size would be important for bioinformatic analysis where the starting material is DNA, the panel was intended for assessing the DNA extraction methodology applied to bacterial cells. With regard to stability, the Committee was assured that despite only 3 months of stability data being currently available, the evidence indicated that the candidate material was very stable and that stability assessments would continue to be performed.

The Committee considered the report of the study (WHO/BS/2023.2455) and recommended that candidate material 22/210 be established as the WHO International Reference Reagent for gut microbiome DNA extraction (whole cell).
7.2 Proposed new projects and updates – standards for use in high-throughput sequencing technologies

7.2.1 Proposed First WHO International Reference Panel for adventitious virus detection in biological products by high-throughput sequencing

HTS is increasingly being used as an alternative to in vivo and in vitro assays for adventitious virus detection in biological products as it is rapid, more sensitive and highly consistent with the 3Rs principles for reducing the use of animals in testing. Following the inclusion of HTS in the latest revision of the ICH Q5A guideline, it is anticipated that more manufacturers and regulators will employ such methodologies for adventitious virus detection. However, the validation and qualification of HTS methods require reference materials to demonstrate the sensitivity and specificity of the key steps in the HTS workflow. At its meeting in October 2020, the Committee had recommended that five live viruses, representing virus families with diverse physicochemical and genomic properties, be established as WHO international reference reagents. Due to a significant increase in the use of HTS technologies since then, these international reference reagents had been rapidly depleted; their replacement was now required.

The proposed WHO international reference panel would consist of vials of each of the viruses previously established as individual international reference reagents along with two additional viruses – a coronavirus (OC43) and a parvovirus (MVM). Increasing the number of vials of each virus to 1000 and expanding the range of viruses in the panel should improve the longevity of the proposed reference standard and broaden the scope of adventitious virus detection by HTS. A collaborative study involving regulators, public health agencies, industry and contract research organizations was being proposed to assess detection of the seven viruses by HTS technologies. The viruses would be spiked at $10^4$ viral copies/mL in a high-titre adenovirus background ($10^9$ viral copies/mL) using independent protocols, sequencing platforms and bioinformatics pipelines. It was anticipated that the collaborative study outcomes would be submitted for consideration by the Committee in March 2024.

Should the WHO international reference panel be established, the current five WHO international reference reagents would need to be very clearly demarcated as separate resources with distinct purposes and having different international standing. This would require their disestablishment and removal of all mention of WHO in their names.

Reflecting on the public health importance of adventitious agent detection in biological products, the Committee noted that the recent identification the porcine circovirus PCV1 in a rotavirus vaccine, and a novel rhabdovirus in Sf9 cells, had served to highlight the advantages of HTS technologies in this area. While noting that the proposed panel would be used in spiking studies carried out as part of method validation, the regulatory acceptability of replacing animal
or cell-based methods with HTS approaches would be determined on a product-by-product basis, and as one element of the overall safety data package. It was anticipated that the composition of the proposed panel would probably not need to be changed going forward as it represented the wide range of viral structures and genome types likely to raise safety concerns for vaccines and biotherapeutics produced in animal cells. Reflecting on the range of HTS methods currently in use or development, and the current lack of a WHO written standard or manual specifically on HTS, the Committee discussed the challenges of introducing HTS methods in LMIC and suggested that the conducting of webinars and workshops might be an important step in improving global access to such technologies.

The Committee endorsed the proposal (WHO/BS/2023.2464) to develop a First WHO International Reference Panel for adventitious virus detection in biological products by high-throughput sequencing.

All reference materials established at the meeting are listed in Annex 3.

8.1  WHO international reference standards for use in public health emergencies

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

The First WHO International Standard for SARS-CoV-2 RNA for NAT-based assays (NIBSC code 20/146) was established in December 2020 to support the urgent development of diagnostic assays in response to the COVID-19 pandemic. Following very high demand for this international standard as a consequence of the level of testing worldwide and the large number of commercial NAT-based assays developed, stocks were now nearing depletion. The continued importance of diagnosing infection with SARS-CoV-2 and the need for diagnostic test manufacturers to meet regulatory requirements mean that demand is expected to continue. In order to ensure ongoing availability and continuity of the unitage, the Committee had endorsed a proposal in October 2022 to develop a replacement international standard.

An international collaborative study involving 22 laboratories in 11 countries had now been conducted to evaluate a candidate material (NIBSC code 22/252) as a direct like-for-like replacement of the first international standard. The candidate material consists of an inactivated pre-VOC isolate of SARS-CoV-2 (BetaCoV/Australia/VIC01/2020). To account for the emergence of novel VOC since 2020, and to reflect the diversity of the commercial molecular assays now available, the study had included more samples and participants than was usual for the evaluation of a replacement standard. Performance was assessed alongside the current international standard and a panel of samples representing five VOC. Forty-seven datasets had been obtained using 34 methods spanning a broad range of both qualitative and quantitative molecular technologies. Overall, the analysis showed that the candidate material performed comparably to the first international standard. Expressed relative to either the first international standard or to its proposed replacement, results were harmonized across the range of technologies used, with no discernible differences observed between the VOC, and improved agreement between the quantitative and qualitative methods. The estimated potency of the candidate material 22/252 relative to the first international standard was $7.78 \log_{10} \text{IU/mL}$, with only a $0.01 \log_{10} \text{IU/mL}$ difference between the quantitative and qualitative methods. Accelerated thermal degradation studies conducted over 6 months indicated good stability of the proposed replacement when stored at $-20\, ^\circ\text{C}$, with a predicted annual loss of
potency of 0.07% and sufficient stability for up to 1 month at 37 °C to be shipped at ambient temperature.

Acknowledging the importance of this replacement standard, the Committee discussed what was known about how well the oligonucleotide primers matched the target sequences in different Omicron variants. Unfortunately, as this is often proprietary information, it was not possible to evaluate this aspect comprehensively. Nevertheless, the Committee accepted that as long as an assay detects a SARS-CoV-2 variant, the proposed standard could be used as a calibrant. It was further noted that a precedent had already been established for this type of calibrant for assays detecting the antigenically diverse HIV and hepatitis C virus.

The Committee considered the report of the study (WHO/BS/2023.2459) and recommended that candidate material 22/252 be established as the Second WHO International Standard for SARS-CoV-2 RNA for NAT-based assays with an assigned unitage of 7.50 log_{10} IU/ampoule.

All reference materials established at the meeting are listed in Annex 3.

9.1 WHO international reference standards for vaccines and related substances

9.1.1 First WHO International Standard for antibodies to Nipah virus for neutralization assays (human, serum); and First WHO International Standard for antibodies to Nipah virus for binding assays (human, serum)

Nipah virus (NiV) is a zoonotic virus belonging to the genus Henipavirus in the Orthoparamyxovirinae subfamily of the Paramyxoviridae. Exposure to infected domestic pigs and fruit products contaminated with the secretions of fruit bats have previously resulted in spillover infections in humans, with subsequent human-to-human transmission events reported. Disease symptoms range from mild or asymptomatic to severe acute respiratory infection and in the most severe cases to fatal encephalitis. NiV typically causes frequent but small outbreaks across Asia – however, the occurrence of human-to-human transmission highlights the pandemic potential of this virus. Although no treatment or vaccine is currently available, a number of promising immunotherapies are in development and two candidate vaccines are in Phase I clinical studies. Due to its pandemic potential and lack of therapeutic or prophylactic medicines, NiV is listed as a priority pathogen by WHO and by the Coalition for Epidemic Preparedness Innovations. Antibody reference materials are essential to support the evaluation of vaccines and the development of serological assays by allowing for the harmonization of data between laboratories and different vaccine developers.

An international collaborative study involving 18 laboratories in nine countries had been conducted to evaluate a candidate material (NIBSC code 22/130) consisting of a freeze-dried pool of serum samples taken from 36 convalescent individuals from Bangladesh and Malaysia. The candidate material was tested for its suitability for use in both neutralization assays (n = 19) and binding assays (ELISA; n = 16) alongside a panel of nine other samples. In accordance with a recent Committee decision that separate WHO reference standards should be established for use in antibody neutralization and antibody binding assays, the same candidate material was assigned two separate codes according to intended assay type (NIBSC codes 22/130nt and 22/130bd respectively). When expressed relative to the candidate material, inter-laboratory variation was significantly reduced for both neutralization assays and ELISAs. Similar reductions in inter-laboratory variability were
also observed separately for live virus and pseudovirus assays. Strain-specific differences between the Malaysian and Bangladeshi strains were not observed, either as recombinant antigens for ELISA or in native NiV or pseudotyped virus-based neutralization assays.

Although the stability of the candidate material was assessed in an accelerated thermal degradation study, it was not possible to predict the percentage loss of potency over time using the Arrhenius model. Nevertheless, based on relative potencies, there was only a small loss of potency observed at the higher temperatures (37 °C and 45 °C) after 6 months. It is proposed that the candidate material be kept at −20 °C for long-term storage but could be shipped at ambient temperature.

The Committee discussed the ability of the candidate material to harmonize assay results for the different NiV strains, and concluded that the absence of differences between strains was probably due to the pooled material including serum from individuals exposed to different strains. Remarking on the lack of serum samples from vaccinated individuals in the absence of a licensed product, the Committee agreed that antibodies produced by convalescent individuals would be a suitable source for a reference standard. The Committee noted that the candidate material had been filled as separate standards (one for virus neutralization assays and the other for antibody binding assays specifically measuring immunoglobulin G against viral glycoprotein) and that the same unitage was being proposed for both. In this instance, this was considered by the Committee to be a good approach to the standardization of both assay types.

The Committee considered the report of the study (WHO/BS/2023.2458) and recommended that: (a) candidate material 22/130nt be established as the First WHO International Standard for antibodies to Nipah virus for neutralization assays (human, serum) with an assigned potency of 250 IU/ampoule; and (b) candidate material 22/130bd be established as the First WHO International Standard for antibodies to Nipah virus for binding assays (human, serum) with an assigned potency of 250 IU/ampoule.

9.1.2 WHO International Reference Reagent for antibodies to Ross River virus for neutralization assays (human, plasma)

Ross River fever is a mosquito-borne disease characterized by fever and joint pain which can result in significant morbidity due to persistent polyarthralgia. Ross River fever is caused by Ross River virus (RRV), an arbovirus and member of the genus Alphavirus in the family Togaviridae. Ross River fever is endemic in Australia, Papua New Guinea and elsewhere in the Pacific region, with occasional infections reported among travellers returning from endemic areas. Serodiagnosis of RRV infection is based on a greater than four-fold rise in antibody titre between paired sera in ELISA, combined with the overall clinical
presentation. In the absence of licensed treatments or vaccines, prevention of RRV infection depends on mosquito control, prevention of bites, use of insect repellents and bednets.

Given the epidemic potential of RRV and the challenge of determining vaccine efficacy in clinical trials, an antibody reference material was needed to facilitate the ongoing development of candidate vaccines for the prevention of RRV infection. The establishment of a WHO international reference reagent would allow for harmonization of the results of virus neutralization and other immunoassays, thereby improving the comparability of results obtained by different laboratories, while also helping to define protective antibody levels. Such a reference material would also improve the standardization of serodiagnostic testing leading to improved understanding of RRV seroepidemiology in Australia and the Pacific region. At its meeting in March 2023, the Committee had endorsed a proposal to develop the WHO international reference reagent now being put forward for establishment.

An international collaborative study involving 10 laboratories in five countries had been conducted to evaluate the suitability of a candidate material (PEI code 1500/19) comprising a lyophilized pool of five donations from anti-RRV immunoglobulin G-positive blood donors to serve as a WHO international reference reagent. Data were obtained using a wide range of virus neutralization assays (using live RRV or pseudoviruses), antibody binding assays (such as ELISA), immunofluorescence tests, microsphere-based assays and haemagglutination inhibition assays. The panel of samples used in the study, including the candidate material, were detected by most of the participating laboratories. Moreover, expressing the results relative to the candidate material harmonized the data obtained using the different virus neutralization assays and immunoassays. The harmonized data also provided evidence of the commutability of the candidate material based on the evaluation of individual donor samples included in the study. As RRV and chikungunya virus are serologically cross-reactive members of the Semliki Forest complex of the Togaviridae family, the samples had included a plasma sample positive for antibodies to chikungunya virus.

Real-time stability studies found that the candidate material 1500/19 was stable for at least 3 years when stored at −20 °C or below, and for at least 1 year at 20 °C, with the latter finding supporting shipment at ambient temperature.

The Committee discussed the reasons for proposing this reference material as a WHO international reference reagent rather than a WHO international standard. Acknowledging that the small and highly specialized nature of the RRV field precluded a large collaborative study, the Committee noted that this would not in itself automatically preclude the prospective establishment of a WHO international standard as this would depend on a number of additional factors, including the quality of the data and test methods as well as the technical maturity of the field.
The Committee considered the report of the study (WHO/BS/2023.2463) and recommended that candidate material 1500/19 be established as the WHO International Reference Reagent for antibodies to Ross River virus for neutralization assays (human, plasma) with an assigned unitage of 500 U/vial. Any correlation between neutralizing antibodies and binding antibodies, including with regard to surrogate markers of protection that could be measured using an alternative type of immunoassay, remained to be determined by further studies.

9.2 **Proposed new projects and updates – vaccines and related substances**

9.2.1 **Proposed WHO international standards for novel oral poliomyelitis vaccines types 1, 2 and 3**

Oral poliomyelitis vaccines (OPVs) have been the mainstay of the WHO Global Polio Eradication Initiative. However, the virus strains used to manufacture OPV are genetically unstable and tend to revert to a neurovirulent phenotype during passage, resulting in vaccine-derived poliovirus outbreaks. To address this issue, genetically modified novel OPVs (nOPVs) with improved genetic stability have been developed. Currently, proprietary in-house reference reagents and standards are used in the potency evaluation of nOPVs during product development and lot release, but the availability of international standards and other reference materials will become increasingly important as more manufacturers develop nOPVs.

The Committee was presented with a proposal to develop WHO international standards for monovalent nOPV1, nOPV2 and nOPV3, as well as a for trivalent nOPV. Fourteen laboratories worldwide had now indicated their willingness to participate in a collaborative study to evaluate such potency standards. However, increasingly stringent biosafety requirements for handling polioviruses and a decline in the number of OPV manufacturers may hamper the recruitment of study participants. It was anticipated that the study outcomes would be submitted for consideration by the Committee in 2025.

Notwithstanding the challenges outlined, the Committee noted the importance of this proposal in the context of global polio eradication efforts and endorsed the proposal (WHO/BS/2023.2464) to develop WHO international standards for nOPV types 1, 2 and 3.

9.2.2 **Update on the commutability of the First WHO International Standard for antiserum to respiratory syncytial virus**

The development of an RSV vaccine is a widely recognized global health priority. As neutralizing antibodies against RSV have been reported to correlate with protection against RSV acute lower respiratory infection, the accurate
quantification of neutralizing activity is crucial for vaccine development. The current First WHO International Standard for antiserum to respiratory syncytial virus (subtype A) was first established in 2017 and subsequently updated in 2019 to include antibodies to RSV subtype B. It is used as a reference standard when evaluating RSV neutralization titres in human serum, successfully reducing inter-laboratory variability in the results obtained using samples from naturally infected adults and children, as well as from volunteers participating in vaccine trials.

The Committee was updated on the outcomes of a collaborative study, involving eight laboratories from the United States and Europe, to assess the commutability of the current WHO international standard (NIBSC code 16/284). Study participants had used their own in-house RSV neutralization assay and virus stocks to evaluate the commutability of both the current WHO international standard and its potential replacement (NIBSC code 16/322) to vaccinee serum samples from clinical trials of different RSV candidate vaccines, and age-stratified paediatric serum samples. Five of the laboratories returned data from neutralization assays against both RSV subtypes. Analysis of the data showed that high inter-laboratory GCV values attributed to differences between assay methods were significantly reduced when neutralization titres were expressed relative to either 16/284 or 16/322, regardless of RSV subtype. These results highlighted the utility of both standards in harmonizing the RSV neutralization titres of vaccine clinical trial sera samples and age-stratified paediatric sera samples across a range of assay formats and across various vaccine platforms/candidates, including pre-F protein subunit vaccines, mRNA pre-F vaccines, post-F protein subunit vaccines and adenovirus vector vaccines.

Commending the quality and importance of this study, the Committee reflected on the possibility that all future collaborative studies should assess commutability. However, it was acknowledged that commutability studies present a number of challenges, including the sourcing of suitable material, linking commutability to clinical decisions and completing such studies in a timely manner so as not to hinder the availability of much-needed WHO measurement standards. The Committee suggested that further discussion of commutability should be included in the agenda of its meeting in March 2024.
Annex 1

WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products

WHO Recommendations, Guidelines and other documents in the field of biological product development and standardization are intended to be scientific and advisory in nature. Each of these documents provides guidance for national regulatory authorities (NRAs), developers and manufacturers of biological products, and others who may have to decide upon appropriate methods for ensuring that such products are safe, reliable and potent. In the case of WHO Recommendations and Guidelines, the guidance provided may, if an NRA so desires, be adopted as definitive national requirements or used as the basis of such requirements.

WHO Recommendations, Guidelines and other guidance documents for biological products are formulated by international groups of experts, and are adopted on the recommendation of the WHO Expert Committee on Biological Standardization. Following adoption, the documents are published in the WHO Technical Report Series as part of the respective full report of the Committee, and as listed in this annex. The full reports of the Committee are freely available for download at https://iris.who.int/. Hard copies of the reports can also be purchased from:

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

In all cases in which a previous version of a WHO Recommendations, Guidelines or other guidance document has been revised and superseded by an updated document, it is of paramount importance that only the latest version of the document is used. All documents listed in this annex are current, with no previous versions shown. The annex has also been arranged alphabetically either by product type or regulatory topic to facilitate easy identification of the most up-to-date document.

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3 Abbreviated in the following pages to “TRS”.
Important note

At its sixty-ninth meeting in 2018, the Committee recommended the immediate discontinuation of any requirement to perform the innocuity test (also known as the abnormal toxicity test or general safety test) in all future WHO Recommendations, Guidelines and other guidance documents for biological products published in the Technical Report Series. The Committee further recommended that any mention of this test in any still current WHO document published prior to 2018 be disregarded (Table 1).

These recommendations represent a significant step towards increasingly science-based regulation and regulatory convergence at the global level, while also promoting the application of the 3Rs principles (Replacement, Refinement, Reduction) by reducing the use of animals in biological product quality control and batch-release testing.

Table 1

<table>
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<tr>
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<td>DT-based combined vaccines</td>
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<td>Hepatitis A vaccines (inactivated)</td>
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<td>Hepatitis B vaccines (recombinant)</td>
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<tr>
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### Table 1 continued

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DT = diphtheria and tetanus; HFRS = haemorrhagic fever with renal syndrome; VLP = virus-like particle; MMR = measles, mumps and rubella.
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⁵ Adopted on the recommendation of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, with significant input from the WHO Expert Committee on Biological Standardization.
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### Recommendations, Guidelines and other documents

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<td>RNA vaccines: messenger; for prevention of infectious diseases</td>
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\(^6\) Adopted on the recommendation of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, with significant input from the WHO Expert Committee on Biological Standardization.
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## Annex 2

Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries

Replacement of Annex 7 of WHO Technical Report Series, No. 1004

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Guidelines 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) and for manufacturers of biological products. If an NRA so desires, these WHO Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA.
Abbreviations

AEFI    adverse event(s) following immunization
COVID-19 coronavirus disease 2019
CTD    Common Technical Document
EUL    WHO emergency use listing
GRelP  good reliance practices
GMP    good manufacturing practice(s)
NCL    national control laboratory
NRA    national regulatory authority
PQ     WHO prequalification
RMP    risk-management plan
tWLA   transitional WHO Listed Authority
VIRAT  vaccine introduction readiness assessment tool
VRAF  vaccine readiness assessment framework
WLA    WHO Listed Authority
1. Introduction

Pandemics and other large-scale disease outbreaks caused by newly emerging or known pathogens affecting many people may result in severe disease burden and can claim millions of lives globally. Pandemics are usually caused by respiratory viruses – however, as such events may in future be caused by other pathogens, WHO continually reviews and updates its list of priority pathogens based on global scientific consensus (1).

Pandemic influenza viruses and newly emerging coronaviruses differ significantly from seasonally circulating viruses. Such viruses may evolve from viruses that previously only circulated in animals (for example, severe acute respiratory syndrome coronavirus 2) or from virus subtypes already circulating in humans (for example the 2009 A(H1N1) influenza (swine flu) virus). Due to lack of previous exposure to such viruses, the human population is considered to be immunologically naïve to them. As a result, pandemics and other large-scale disease outbreaks (such as the recent Ebola, Zika and cholera outbreaks) result in an urgent need for medical countermeasures, including vaccines, to limit their spread.

One of the highest priorities in ensuring global health security and protecting public health is to identify strategies that shorten the time required between the emergence of a pandemic virus or other human pathogen and the availability of safe and efficacious vaccines. Therefore, in the event of a pandemic or other public health emergency, the national regulatory authorities (NRAs) of vaccine-importing countries are strongly encouraged to apply procedures based on recognition of, or reliance on, the product evaluation and decisions made by reference NRAs, which may include the NRA of the vaccine-producing country.

The WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines (2) were adopted in 2007 on the recommendation of the WHO Expert Committee on Biological Standardization. Following the subsequent 2009 H1N1 influenza pandemic, a lack of regulatory preparedness was identified as one of the factors that had delayed or in some cases prevented the deployment of pandemic influenza vaccines in importing countries. This was especially the case for vaccines intended for donation or deployed by United Nations agencies in response to the pandemic (3, 4). Therefore, the WHO Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries (5) were developed to provide guidance on appropriate regulatory approaches to the marketing authorization of such vaccines, and on their lot release during a public health emergency. These guidelines were developed in the context of the Pandemic Influenza Preparedness (PIP) Framework’s Partnership contribution implementation plan 2013–2016 for regulatory capacity-building and strengthening of pandemic preparedness and response (6).
Following the subsequent Ebola epidemic and coronavirus disease 2019 (COVID-19) pandemic, a need was identified to update the published guidelines and expand their scope to cover all vaccines used in pandemics or other public health emergencies, and to draw on the lessons learned during these emergencies. Furthermore, WHO global benchmarking tool assessments used to objectively evaluate national regulatory systems indicated a need to strengthen regulatory preparedness in countries for the timely approval of medical products during public health emergencies (7). Recently published or updated WHO guidelines and other guidance documents include:

- Good regulatory practices in the regulation of medical products (8);
- Good reliance practices in the regulation of medical products: high level principles and considerations (9);
- Guidelines on import procedures for medical products (10); and
- Guidance on development and implementation of a national deployment and vaccination plan for pandemic influenza vaccines (11).

Many of the principles outlined in these and other guidance documents have been incorporated into the current Guidelines.

2. Purpose and scope

This document provides guidance to NRAs of vaccine-importing countries (including countries supplied with vaccines through United Nations agencies, programmes and funds and/or other international/regional mechanisms, countries receiving donations of vaccines and countries which self-procure vaccines) on the regulatory oversight of vaccines used during pandemics or other public health emergencies. However, the principles set out may also apply to other medical products urgently needed during a pandemic or other public health emergency.

The aim of the document is to help such countries in preparing and establishing processes to expedite the provision of an authorization or emergency approval to use a hitherto unauthorized vaccine in an emergency, as well as to manage post-authorization procedures.

It is recognized that countries will already have national legislation and policies on the regulation of vaccines. Some countries may also have regulations in place on accepting donations of vaccines and ancillary products. Therefore, the current document is intended to provide general guidance and principles to the NRAs (or other bodies with appropriate legislative powers) of importing countries for evaluating vaccines specifically for use during a pandemic or other
public health emergency, and on establishing authorization procedures for the use of such vaccines.

A strong emphasis has been placed on the need to put in place risk-based decision-making processes that minimize duplication and make life-saving vaccines available for use without unnecessary delays during pandemics or other public health emergencies.

The document is intended for use by NRAs but will also be of interest to national immunization technical advisory groups, as well as to manufacturers and authorities in the private and public sectors responsible for importing, planning and managing vaccine deployment and vaccination operations at all levels. The current document should be used together with other relevant WHO guidelines.

3. Terminology

The following definitions apply to the terms as used in these WHO Guidelines. These terms may have different meanings in other contexts.

**Authorization**: an umbrella term which includes all types of authorization that may be given by an NRA regarding the use of a vaccine during a pandemic or other public health emergency. The authorization may refer to a marketing authorization or to an emergency authorization as defined below.

**Emergency authorization**: an early access mechanism with time limitation used by regulatory authorities to expedite the availability of new investigational/unauthorized vaccines during a pandemic or other public health emergency. In principle, this is granted if the known and potential benefits of the vaccine are considered to outweigh the known and potential risks, and upon meeting certain criteria (for example, that no alternative products are approved or available). In some jurisdictions, this is referred to as “emergency use authorization” or “conditional approval”.

**Emergency use listing (EUL)**: a risk-based procedure used by WHO to assess and list unlicensed vaccines with the aim of expediting their availability during a pandemic or other public health emergency. It is expected that a manufacturer that applies for WHO EUL assessment of a vaccine will complete the development of the product prior to its submission for full marketing authorization and WHO prequalification (PQ) in the future.

**Import authorization**: the process undertaken by the NRA or designated institution to approve or authorize the importation of a vaccine into the country.

**Importing country**: a country that imports a vaccine produced in another country.

**Interpandemic phase**: the period between pandemics (12).
Joint review: a form of work-sharing in which a regulatory task such as the review/assessment of a vaccine is conducted by two or more NRAs in collaboration.

Marketing authorization: a procedure that is conducted by an NRA for the approval of a vaccine for marketing and use in the country, and which includes a process of evaluation to determine the quality, safety and efficacy of the product, the benefit–risk ratio and the appropriateness of the product information. This term may also be referred to as “licensing” or “registration” in other documents (13).

National pandemic preparedness plan: a national plan that aims to set out country-specific priorities and actions, and to identify the major components that must be put in place (for example, coordination, resource identification and allocation, and capacity-building) along with the capacities that should be strengthened to respond to a pandemic (14).

Pandemic phase: the period of global spread of a disease caused by a new virus (or new virus strain) or other pathogen. Progression from the interpandemic phase to the pandemic phase may occur quickly or gradually, as indicated by the global risk assessment principally based on virological, epidemiological and clinical data (12).

Pandemic preparedness vaccine: a vaccine developed and tested in anticipation of a pandemic, and manufactured using a virus strain believed to have similar characteristics to a potential pandemic virus strain (also referred to as “mock-up pandemic vaccine” or “vaccine against a novel virus” in other documents) (2, 15, 16).

Pandemic vaccine: a vaccine designed for use against a virus or other pathogen identified by WHO as the causative agent of a pandemic.

Prequalification (PQ): a procedure in which WHO applies international standards to comprehensively evaluate and determine whether vaccines are safe, effective and of adequate quality in order to advise United Nations agencies and countries on the suitability and acceptability, in principle, of vaccines being considered for purchase.

Public health emergency: an extraordinary event that is determined, as provided in the International Health Regulations (17), to: (a) constitute a public health risk to other States through the international spread of disease; and (b) potentially require a coordinated international response.

Recognition: a specific and formalized type of reliance in which an NRA (the relying NRA) accepts the regulatory decision of another NRA (the reference NRA) or the recommendation of a trusted institution (such as WHO). Recognition should be based on evidence that the regulatory requirements of the reference NRA or recommendations given by a trusted institution are sufficient to meet the regulatory requirements of the relying NRA. Recognition between NRAs may be unilateral or mutual and may, in the latter case, be the
subject of a mutual recognition agreement. The relying NRA remains responsible and accountable for decisions taken even when it recognizes the regulatory decisions of the reference NRA or the recommendations of a trusted institution.

**Reference NRA**: an NRA whose work or decisions are relied upon by the NRA of an importing country for the authorization and life-cycle management of vaccines used during a pandemic or other public health emergency. The choice of a reference NRA could be based on WHO Listed Authority (WLA) status, including transitional WLA (tWLA) listing (18), the designation of WHO maturity level 3 or 4 status, consultation with WHO, or other criteria acceptable to the NRA of the importing country. The WLA and tWLA listings can be found on the WHO website.7

**Reliance**: the act whereby a relying NRA takes into account and gives significant weight to assessments performed by another NRA (the reference NRA) or to recommendations given by a trusted institution (such as WHO), or to any other authoritative information, in reaching its own decision. The relying NRA remains independent, responsible and accountable for the decisions taken by it, even when it relies on the decisions, recommendations, assessments and information of the reference NRA or other trusted institution.

**Relying NRA**: an NRA that accepts, takes into account and/or gives significant weight to the decisions of a reference NRA, the recommendations of a trusted institution (such as WHO) and/or to the assessments performed by them, in reaching its own regulatory decisions.

**Risk-management plan (RMP)**: a plan containing information on a vaccine’s safety profile and on the measures to be taken to prevent or mitigate any risks associated with its use. The RMP is submitted by manufacturers as part of the marketing authorization dossier that is evaluated by regulatory authorities before a vaccine can be authorized, and is regularly updated by the manufacturer as new information becomes available.

**Variant**: an evolved virus that differs in its genetic information (that is, in its genome sequence) compared to the original virus.

**WHO Listed Authority (WLA)**: a regulatory authority globally recognized to be operating at an advanced level of performance, thereby replacing the procurement-oriented concept of “stringent regulatory authority”. The tWLA is a list of all regulatory authorities on the public WHO List of transitional WLAs (18). These NRAs are recognized by WHO to have achieved levels of operation necessary for the regulation of vaccines. The WHO List of tWLA is valid for 5 years from the date of publication of the final WLA Operational Guidance, during which time authorities will be evaluated against

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the requirements for designation as a WLA. A regulatory authority will move from tWLA to permanent WLA status upon successful completion of the WLA evaluation process.

4. General considerations

Countries should have a legal framework in place that requires all vaccines to be approved for use. However, marketing authorization of vaccines is not always possible during emergency situations and thus NRAs may need to authorize the use of vaccines following an expedited risk-based assessment of their public health needs. In the interpandemic phase, countries should review, and if necessary amend, existing legislation to allow for flexibility by the NRA in choosing an authorization pathway that addresses public health needs. The legal framework should be flexible enough to enable the NRA to apply recognition of, or reliance on, the decisions and work of reference NRAs and/or WHO recommendations for prequalification and/or emergency use listing (PQ/EUL), or to conduct a risk-based review of available safety, efficacy and quality data (see section 5 below for more details on each of these approaches).

All countries should prepare for public health emergencies, including pandemics, that may cause high morbidity and mortality, and lead to considerable social disruption. In 2013, WHO published updated pandemic preparedness guidance to reflect experience gained and lessons learned from the 2009 H1N1 influenza pandemic, and to support further preparedness efforts at national and subnational levels (12). The updated guidance sets out a risk-based approach that: (a) enables a more flexible response to different scenarios; (b) emphasizes the key importance of multisectoral and whole-of-society involvement in planning; and (c) uses a simplified pandemic phase structure that includes the interpandemic and pandemic phases.

Regulatory preparations for a pandemic or other public health emergency should be undertaken in order to strengthen the legal and regulatory framework, and to enable flexibility in the enforcement of requirements for importing and approving or authorizing a vaccine in emergency situations. This would include clearly defining the regulatory pathways to be used for the emergency authorization or marketing authorization of a new vaccine under emergency conditions (11). The WHO global benchmarking tool, whether through a formal process or a self-assessment process, can be used to identify gaps in the regulatory system and to ensure that countries have adequate oversight and capacities to regulate vaccines. This tool can be used in addition to other mechanisms for evaluating capacities under emergency situations such as the COVID-19 vaccine introduction readiness assessment tool (see section 4.1 below).
NRAs together with national immunization programmes, marketing authorization holders and other stakeholders should also develop strategies for enhanced post-authorization surveillance to monitor the safety and minimize the risks of vaccines used during a pandemic or other public health emergency. Such strategies should include considerations on risk communication and risk-management plans (RMPs), which are requirements of the marketing or emergency authorization process and often include post-authorization studies to further characterize important potential risks and to evaluate safety in special populations (for example, children, pregnant women, lactating women, immunocompromised individuals and people with pre-existing health conditions). As RMPs would also usually include reference to all ongoing studies including those in other countries, vaccine-importing countries should in the interpandemic phase evaluate legislative/regulatory requirements for post-authorization safety studies with the aim of reducing duplication and allowing for risk-based determination of the adequacy of data from other countries during a pandemic or other public health emergency. Detailed WHO guidance on safety monitoring and post-authorization surveillance procedures is provided in:

- Guidelines on regulatory preparedness for human pandemic influenza vaccines (2);
- Global manual on surveillance of adverse events following immunization (19);
- COVID-19 vaccines: safety surveillance manual (20); and
- Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification (21).

The emergency procedures should also include processes for ensuring information management and effective communication, as well as cooperation, between different branches of the NRA and relevant stakeholders such as public health authorities, the national immunization programme, disease management programmes, the marketing authorization holder and others. (11, 22). Communication with other NRAs may also be necessary.

Plans should be developed and transparently shared with all stakeholders to address the need for official communication from the NRA relevant to specific audiences such as the general public, health care workers, national and subnational authorities, industry and international collaborators when needed. The principles set out in relevant WHO guidelines (23–25) should be followed. Communication and information-sharing systems should be established and implemented for all stakeholders (11). Prior to a pandemic or other public health emergency, these systems should be tested to build trust with the population and other audiences.
4.1 The role of the NRA in the national pandemic and emergency preparedness plan

A national pandemic and emergency preparedness plan should be developed and endorsed before a pandemic or other public health emergency arises. The plan should include acknowledgement of the roles and responsibilities of the NRA in the regulatory oversight of vaccines (11, 26).

Most countries developed and published their national pandemic influenza preparedness plans in 2005 and 2006, and updated them following the 2009 H1N1 influenza pandemic. During the COVID-19 pandemic, countries also used the vaccine introduction readiness assessment tool (VIRAT) to develop a roadmap to prepare for vaccine introduction and to identify gaps and areas for potential support – along with the vaccine readiness assessment framework (VRAF) to obtain granular information on gaps and associated costs, thus enabling the programming of financial resources for vaccine deployment. The VIRAT and VRAF tools have now been consolidated into the comprehensive COVID-19 vaccine introduction readiness assessment tool (VIRAT/VRAF 2.0) developed in 2020 (27).

Where necessary, countries should expand the scope of their national pandemic and emergency preparedness plans to cover any potential regulatory activities during a pandemic or other public health emergency. The national plan should be aligned with any existing regional or continent plans where possible. The plan should include strategies to facilitate the timely availability, distribution and administration of vaccines, while ensuring their quality, safety and efficacy.

4.2 Considerations for national regulatory preparedness

The NRA should be responsible for developing and implementing the following procedures to support the national pandemic and emergency preparedness plan and national vaccine deployment plan before a pandemic or other public health emergency arises (11).

4.2.1 Strengthening the regulatory system

- Mapping of existing regulatory processes and capacities in relation to recommended international standards such as the WHO global benchmarking tool, and implementing interventions to close identified gaps and strengthen the importing country’s regulatory system, particularly the sub-indicators related to regulatory preparedness.

- Developing a robust quality management system articulating risk-based thinking (28) and good reliance practices (GRelP) including information-sharing procedures, as appropriate, between the
importing country’s NRA and selected reference NRAs in the event of a pandemic or other public health emergency.

- Mapping of existing national, legal and regulatory frameworks for research, including other organizations that collaborate with the NRA in the approval of clinical trials (for example, an ethics committee) to support the conducting of such trials for novel vaccines, if required.
- Allocating resources to be used when a pandemic alert or other public health emergency has been declared by WHO and/or the responsible national authority.

4.2.2 Accelerating review and authorization

- Identifying potential reference NRAs/trusted institutions (for example, WHO) and establishing partnerships and collaboration with them as far as possible, for example through the signing of memoranda of understanding.
- Developing a system to accelerate the authorization of pandemic or other emergency use vaccines, and ensure the optimization of available resources in response to the pandemic or other public health emergency, that includes:
  - definition of regulatory pathways for review and/or approval (see section 5.1 below);
  - definition of requirements for the dossier or supporting documents required for evaluation by the NRA under the different regulatory pathways (see section 5.2 below);
  - a process allowing for recognition of the decision of, or reliance upon the expertise of, a reference NRA;
  - a process for granting emergency authorization of vaccines, including reliance on the WHO EUL procedure, when appropriate;
  - a process for expediting marketing authorization of vaccines recommended under WHO PQ, when appropriate;
  - a procedure for marketing authorization or emergency authorization of the pandemic or other emergency use vaccine through an independent review by the NRA of the vaccine-importing country if recognition or reliance cannot be implemented;
  - preparation of templates for emergency benefit–risk consideration and assessment reports during an emergency; and
– a procedure for granting authorization to pandemic preparedness vaccines, if applicable.

- Developing procedures for joint review within established collaboration networks or through collaboration with reference NRAs and WHO.

### 4.2.3 Establishing an advisory group/committee that includes external experts

- Establishing procedures for the identification and timely appointment of an emergency evaluation task team for pandemic or other emergency use vaccines comprising experts in the country (and if possible, in the region and continent) in different fields (for example, virologists, immunologists and disease experts) from academia, the ministry of health and/or the private sector to:
  - support the evaluation of the candidate vaccine(s);
  - recommend appropriate regulatory authorization of suitable vaccines and provide advice to decision-makers; and
  - allow for the regular review of task team appointments and procedures (for example, during the interpandemic phase).

- Developing a procedure for the expedited approval of the NRA recommendation by other authorities within the country (for example, the ministry of health or a national advisory committee), if required.

### 4.2.4 Establishing post-authorization procedures

- Developing mechanisms for approving and communicating post-authorization changes for vaccines authorized in a pandemic context – for example, through labelling indicating extension of shelf-life, language(s) available, safety, dosage, age, indication and other information (13).

- Establishing a robust system and procedure for the importation of pandemic or other emergency use vaccines, including incorporation of importation pre-advice from the NRA to importers where possible (for example, proposed target timeline of not more than 5 working days).

- Establishing procedures and requirements for lot release of pandemic or other emergency use vaccines by the NRA during the pandemic phase or public health emergency by adopting recognition mechanisms (see section 6.4 below).
- Establishing a procedure for keeping a record of the distribution of product batches, regardless of the route of acquisition, to facilitate traceability – this may include the use of a 2D barcode on the secondary packaging.
- Outlining post-authorization surveillance procedures, which should include special provisions for post-authorization surveillance of the pandemic or other emergency use vaccine, including any AEFI, in accordance with the RMP.
- Ensuring system preparedness for implementing potential RMP elements and/or meeting the conditions of product approval (for example, a requirement for post-approval trials in special populations, if applicable).

4.2.5 External communications

- Selecting an NRA contact point for communications with WHO, other regulatory authorities and other stakeholders (including national immunization programmes and marketing authorization holders) on public health/regulatory issues.
- Developing a public communications plan summarizing the basis for decision-making.
- Establishing procedures for interacting with the public health agencies that will procure, deploy and administer the vaccines, including discussion of options for the appropriate sourcing of vaccines.

The national pandemic and emergency preparedness plan and national vaccine deployment plan should be reviewed and tested regularly to ensure that they are up to date.

4.2.6 Labelling requirements

Although legal requirements for labelling vary at the national level, the NRAs of vaccine-importing countries are encouraged to exercise flexibility during a pandemic or other public health emergency to enable the timely distribution of vaccines – for example, by waiving requirements for the inclusion of local languages. NRAs are also encouraged to allow the use of a common international label for pandemic or other emergency use vaccines carrying the following minimum information, as recommended in the WHO Model packaging for COVID-19 vaccines (29) to ensure the safe use of the vaccines:

- Name of the vaccine
- Type of vaccine
- Method/route of administration
- Dose/concentration
- Storage information
- Lot number
- Name of marketing authorization holder/manufacturer
- Manufacture date
- Expiry date (to be confirmed using a QR code).

NRAs may also consider allowing inclusion of the statement “For Pandemic or Emergency Use Only” on labels to differentiate a vaccine approved under the emergency authorization procedure from vaccines with regular marketing authorization.

While the use of a QR code is recommended to confirm the expiry date during a pandemic or other public health emergency, it is acknowledged that in some regions, legislation requires the printing of expiry dates on the label (30). Therefore, to avoid premature disposal and wasting of vaccines during a pandemic or other public health emergency, the NRA should have a mechanism in place (based on use of a QR code or other approach) for communicating up-to-date information on the expiry date in a timely manner to the national immunization programme, health care professionals and the public, as the shelf-life of the vaccine may be extended after initial authorization of the vaccine following the generation of real-time stability data. Further guidance on leveraging technologies for automated product traceability and information sharing can be found in the relevant WHO guidelines (30).

5. Risk-based considerations for regulatory evaluation and authorization

The NRAs of vaccine-importing countries are strongly encouraged to exhibit flexibility and to apply a risk-based approach to ensure the timely evaluation and authorization of quality assured vaccines during a pandemic or other public health emergency. A risk-based approach takes into consideration factors such as whether a vaccine has been approved by a reference regulatory authority or recommended by other trusted institutions (such as WHO), the phase of a pandemic (if applicable) and the risk to the population based on the potentially limited quality, safety and efficacy data available for a vaccine during an emergency situation. Such an approach also supports the optimizing of resources, which are often stretched during a pandemic or other public health emergency.

The NRA of an importing country should consider relying on the product evaluation and decisions made by reference NRAs, which may include
the NRA of the vaccine-producing country, or on the recommendations of WHO or other trusted institution. The sameness of the product being submitted to the relying authority and the product approved by the reference regulatory authority should always be considered as part of the evaluation process. All relevant aspects of sameness should be considered, including same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same suppliers of active pharmaceutical ingredient and same excipient quality. Additionally, the results of supporting studies of vaccine quality, safety and efficacy, indications and conditions of use should in general match those obtained by the NRA upon which the importing country NRA is relying (9). Depending on the level of reliance, the NRA may also require further data to confirm the applicability of the assessment outcome in their national context, or may perform an abridged assessment (9).

Importing countries should select, and where possible establish links with, suitable reference NRAs and other trusted institutions during the interpandemic period. The NRA of the importing country should establish mechanisms and procedures for relying on the authorization decisions of the NRA of the country producing the vaccine, or other reference NRA, or on WHO recommendations for PQ/EUL, as appropriate, when considering approving a vaccine for use in a pandemic or other public health emergency. Such reliance mechanisms and procedures may involve the signing of a memorandum of understanding or recognition agreement during the interpandemic phase, and may include information-sharing procedures between the importing country NRA and selected reference NRAs. Countries may also rely on the outcome of the review of vaccines assessed by WHO and recommended under the PQ/EUL procedures.8

The unredacted assessment reports, public assessment reports, inspection reports and RMPs from other NRAs may provide valuable insights depending on the level of reliance, and may inform the decision-making processes of NRAs in importing countries. Manufacturers and reference NRAs are encouraged to share, in line with their national laws, relevant unredacted assessment and inspection reports, as well as RMPs, with the NRAs of importing countries to facilitate the use of reliance pathways. If these reports are not readily available, direct communication with the relevant NRA or WHO (in the case of WHO PQ/EUL vaccines) is strongly encouraged.

Another risk-based approach that countries may use is work-sharing through joint reviews. Procedures for joint review of a pandemic or other

8 More information on the WHO EUL procedure for vaccines can be found at: https://www.who.int/teams/regulation-prequalification/eul/eul-vaccines.
emergency use vaccine dossier by countries participating in established collaboration networks or in collaboration with reference NRAs should be developed as part of regulatory preparedness. This may include forecasting the use of an accelerated form of an existing joint review model and/or the signing of advance agreements with potential new collaborators during the interpandemic phase.

Even when using reliance, NRAs should have access to all available quality, safety and efficacy data, RMPs, and reference assessment and inspection reports to facilitate informed decision-making and to strengthen regulatory oversight of the vaccine after its introduction. When reliance cannot be implemented, a pre-submission meeting with the manufacturer may be useful in expediting the availability of a pandemic or other emergency use vaccine as this will provide an opportunity for the manufacturer to receive technical advice from the NRA when compiling their submission, thereby reducing the review time once a dossier is submitted. The NRA should also conduct an appropriate review of the documentation submitted and document the extent of the available evidence on which the recommendation to approve or reject was based, even during a pandemic or other public health emergency. However, every effort should be made to do this in a timely manner.

As was noted during the COVID-19 pandemic, it may not be possible for manufacturers to submit applications for authorization to all countries in the midst of a public health emergency. During that event, WHO acted as a “facilitator” for the provision of relevant quality, safety and efficacy data to NRAs under relevant confidentiality agreements between WHO and the manufacturers, and between WHO and the NRAs. RMPs, and assessment and inspection reports were provided to NRAs to facilitate decision-making and future regulatory oversight of the vaccine. A similar model should be considered for use during any future pandemic or other public health emergency.

5.1 **Selection of an appropriate regulatory pathway**

As summarized in Fig. 1, a risk-based approach should be taken when selecting the appropriate regulatory pathway for authorization of pandemic or other emergency use vaccines. In some situations, an application for authorization of such vaccines may be submitted in parallel to the reference NRA or WHO and to the NRA of the importing/relying country. Under these circumstances, the NRA of the importing countries are encouraged to take into consideration the findings or outcomes of the review of the reference NRA or WHO when conducting their own review.
5.2 Documentation required according to regulatory pathway

Reliance ranges from full recognition of the decision of a reference NRA or of the recommendation of a trusted institution such as WHO, using minimum documentation, to the use of full unredacted assessment reports and/or additional data or information to make an independent decision. The extent of reliance applied and documentation required will be decided upon by countries in line with their regulatory capacities and legal frameworks. Guidance on the documentation to be requested under the various pathways available for the approval of pandemic or other emergency use vaccines is provided below and summarized in Table 1. It is possible that not all documentation for a vaccine will be available at the time of application, and many NRAs allow applicants to submit evidence as it becomes available, for example, using written commitments. Although reliance is not limited to marketing authorizations and inspections, the current section focuses on reliance for these functions.

5.2.1 Recognition

This approach is the process of recognizing the decision of a reference NRA or the recommendation for PQ/EUL by WHO, supported by verification of product sameness (9) but without further technical evaluation. This approach can also be referred to as a verification review. Where it has been agreed (as defined in the approved NRA pandemic or other public health emergency procedures) that the
decision of a reference NRA or WHO recommendation for PQ/EUL can be used as the basis of a recommendation for authorization, this approach would involve acceptance based on the use of the evaluation and terms of authorization from the reference NRA or WHO. The relying NRA retains sovereignty of, and has responsibility for, the final decision, and therefore some degree of difference (for example, in product information) is possible.

5.2.1.1 Documentation required

- certificate or other evidence of the reference NRA’s authorization decision, or the WHO recommendation for PQ/EUL;
- (public) assessment and inspection reports (if available);
- unredacted assessment and inspection reports of the reference NRA as far as possible, and in accordance with its national laws or with WHO PQ/EUL (and if required by the importing country’s legal framework); and
- any other documentation required by the importing country’s legal framework.

5.2.1.2 Applicability

During an emergency situation, this approach would be applicable for a pandemic or other emergency use vaccine authorized by a reference NRA or recommended by WHO for PQ/EUL. It may also be applicable during the pandemic phase to a pandemic vaccine authorized by the NRA of the producing country regardless of maturity level.

5.2.2 Reliance

This approach involves relying on the assessments, inspections and/or decisions of other competent NRAs or on a WHO recommendation for PQ/EUL in order to conduct abridged reviews. Reliance may be placed on reference NRAs or trusted institutions using, for example, assessment reports. Where it has been agreed (as defined in the approved NRA pandemic or other public health emergency procedures) that the decision, recommendation or work from another NRA or trusted institution can be considered and used as the basis of a recommendation for authorization by importing countries, this approach would involve the abridged review and use of the terms of authorization of the reference NRA or recommendation by WHO. The vaccine supplied should be the same as that approved by the reference NRA (9). The relying NRA retains sovereignty of, and has responsibility for, the final decision, and therefore some degree of difference is possible.
5.2.2.1 Documentation required

- certificate or other evidence of the reference NRA’s authorization decision, or the WHO recommendation for PQ/EUL;
- (public) assessment and inspection reports (if available);
- unredacted assessment and inspection reports of the reference NRA as far as possible, and in accordance with its national laws or with WHO PQ/EUL; and
- Common Technical Document (CTD) dossier or documentation essentially the same as that submitted to the reference NRA or WHO as specified in published WHO guidance on GreIP (9).

5.2.2.2 Applicability

This approach would be applicable during the interpandemic and pandemic phases for a pandemic vaccine authorized by a reference NRA or recommended by WHO for PQ/EUL. It may also be applicable during the pandemic phase to a pandemic vaccine authorized by the NRA of the producing country regardless of maturity level.

5.2.3 Emergency authorization

Emergency authorization is an early access mechanism used to expedite the availability of new investigational/unauthorized vaccines during a public health emergency. It is granted if it is reasonable to believe that: (a) the vaccine may be effective based on the totality of evidence available; (b) the known and potential benefits outweigh the known and potential risks; and (c) certain criteria have been met – for example, the absence of approved or available alternatives.

Emergency authorization is a fast-track process based upon review of the information available at the time, or reliance on the decision of a reference NRA or WHO EUL recommendation. If a fast-track review is deemed appropriate (as defined in the approved NRA pandemic or other public health emergency procedures), the documents listed below should be reviewed.

A vaccine is given an emergency authorization for a limited period and with certain conditions, mostly related to obtaining post-authorization data such as AEFI and other quality, safety and efficacy data for further extension of the authorization period (if required). Once adequate data have been generated, the full application dossier should be provided for review and authorization.
5.2.3.1 **Documentation required**

If recognition or reliance is to be used:

- unredacted assessment and inspection reports of the producing country’s NRA or reference NRA as far as possible, and in accordance with national laws, or the WHO EUL recommendation; and
- CTD dossier or documentation essentially the same as that submitted to the reference NRA or WHO as specified in published WHO guidance on GreIP (9).

If a fast-track independent review is to be conducted:

- evidence of quality (certificate of analysis or lot release) and good manufacturing practice (GMP) certificate; and
- the available documentation or format of a dossier necessary to demonstrate that vaccine quality, safety and efficacy are acceptable in the context of a public health emergency if the CTD dossier is not available.

5.2.3.2 **Applicability**

This approach would be applicable during a pandemic or other public health emergency for a vaccine given a WHO EUL or authorized by the producing country’s NRA or by a reference NRA.

5.2.4 **Independent review of the full dossier**

This is the standard process of evaluation of the full dossier for marketing authorization for vaccines that are new applications or that were previously authorized by NRAs other than a reference NRA.

5.2.4.1 **Documentation required**

The documentation should be complete, as legally required in each country – for example, Modules 1–5 of the CTD dossier.

5.2.4.2 **Applicability**

Independent full review would usually be applicable to vaccines authorized in the interpandemic phase. During a pandemic phase, if a full review is performed, adequate resources should be made available to ensure that the review is completed in a timely manner. This would require evaluation of the documentation of product quality, as well as of the results of nonclinical and clinical studies to demonstrate safety and efficacy in the target population. The documentation reviewed should be in line with national legal requirements.
The review will result in the issuance of marketing authorization if all conditions are met.

It is possible that not all documentation for a vaccine will be available at the time of application, and many NRAs allow applicants to submit evidence as it becomes available. This approach is generally known as a “rolling review” (31) and is intended to shorten the time to market for novel vaccines.

Where applicable, and in the interpandemic period, the NRA of an importing country may conduct a full pandemic preparedness vaccine dossier review to ensure familiarity with the characteristics of such vaccines prior to the next pandemic phase.

Table 1
Summary of the documentation required for the different pathways available for the authorization of pandemic or other emergency use vaccines

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Documentation required</th>
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<tbody>
<tr>
<td>Recognition</td>
<td>• Certificate or other evidence of the reference NRA’s authorization decision, or the WHO recommendation for PQ/EUL.</td>
</tr>
<tr>
<td></td>
<td>• (Public) assessment and inspection reports (if available).</td>
</tr>
<tr>
<td></td>
<td>• Unredacted assessment reports of the reference NRA in accordance with its national laws or with WHO PQ/EUL (and if required by the importing country’s legal framework).</td>
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<tr>
<td></td>
<td>• Any other documentation required by the importing country’s legal framework.</td>
</tr>
<tr>
<td>Reliance</td>
<td>• Certificate or other evidence of the reference NRA’s authorization decision, or the WHO recommendation for PQ/EUL.</td>
</tr>
<tr>
<td></td>
<td>• (Public) assessment and inspection reports (if available).</td>
</tr>
<tr>
<td></td>
<td>• Unredacted assessment and inspection reports of the reference NRA as far as possible, and in accordance with its national laws or with WHO PQ/EUL.</td>
</tr>
<tr>
<td></td>
<td>• CTD dossier or documentation essentially the same as that submitted to the reference NRA or WHO as specified in published WHO guidance on GReIP (9).</td>
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Table 1 continued

<table>
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<tr>
<th>Pathway</th>
<th>Documentation required</th>
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<tr>
<td>Emergency authorization</td>
<td>If recognition or reliance is to be used:</td>
</tr>
<tr>
<td></td>
<td>• Unredacted assessment and inspection reports of the producing country’s NRA or reference NRA as far as possible, and in accordance with national laws, or the WHO EUL recommendation.</td>
</tr>
<tr>
<td></td>
<td>• CTD dossier or documentation essentially the same as that submitted to the reference NRA or WHO as specified in published WHO guidance on GReLP (9).</td>
</tr>
<tr>
<td>If a fast-track independent review is to be conducted:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Evidence of quality (certificate of analysis or lot release) and GMP certificate.</td>
</tr>
<tr>
<td></td>
<td>• The available documentation or format of a dossier necessary to demonstrate that vaccine quality, safety and efficacy are acceptable in the context of a public health emergency if the CTD dossier is not available.</td>
</tr>
<tr>
<td>Independent review of the full dossier</td>
<td>• Modules 1–5 of the CTD dossier.</td>
</tr>
</tbody>
</table>

5.3 **Decision-making**

Before a regulatory decision to recommend authorization of a pandemic or other emergency use vaccine is taken, the NRA should ensure that the following conditions are met:

- The benefit–risk ratio is deemed favourable – that is, the known and potential benefits outweigh the known and potential risks based on evaluation of the available data – and this can be communicated in a comprehensive and transparent manner.
- An adequate document package was provided, and a commitment obtained from the manufacturer to provide any outstanding information related to vaccine quality, safety or efficacy post authorization as it becomes available.
- An RMP has been reviewed and approved.
- The packaging, label and package insert meet national requirements and are in line with the guidance provided in section 4.2.6 above.

The evaluation may need to be based upon minimal and incomplete documentation, and this should be acknowledged in the recommendation. An evaluation report should be produced by the NRA under all the review pathways.
in line with published WHO guidance on good regulatory practices in the regulation of medical products (8). During a pandemic or other public health emergency, emergency approval procedures may be used. Approval may be based upon limited clinical and/or quality data (for example, stability data) and upon expedited evaluation of the available evidence. Therefore, the approval may include one or more special conditions for use, including:

- use only during the period of the pandemic or other public health emergency;
- use only in certain specified groups at high risk;
- special conditions for post-authorization safety reporting; and
- requirement for evidence generation to address knowledge gaps.

In some countries, the NRA may have the authority to approve the use of a vaccine without reference to another national authority, while in other countries a final approval or directive (for example, from the ministry of health or a national advisory committee) may be required in addition to the NRA review.

6. Post-authorization activities

6.1 Post-authorization changes

Vaccines typically undergo numerous changes after authorization for reasons such as better understanding of the product and manufacturing process, the scale-up of batch quantities, additional manufacturing sites, and the availability of additional data or information resulting from product use in wider populations. One common change submitted after authorization is the extension of use of the vaccine to other groups or populations that were not included in the initial clinical indication.

As with all newly approved vaccines there will be changes submitted to the NRA following the initial authorization of pandemic or other emergency use vaccines. NRAs and manufacturers are encouraged to follow the guidance provided in the WHO Guidelines on procedures and data requirements for changes to approved vaccines (13). The review and approval process should be prioritized, and timelines reduced in a pandemic or other public health emergency, and existing global initiatives leveraged to streamline reviews. Manufacturers should always be requested to supply the updated or latest version of the product information with the vaccine, and to publish the same on their website so that the end users in the importing country have access to all updates, changes or variations to the product information that may have been made since the initial authorization.
Changes that may be of crucial importance to importing countries during a pandemic or other public health emergency include safety and efficacy changes, as well as changes in the shelf-life and “in use” stability of the vaccine. Continued evaluation of the benefit–risk profile of the vaccine should be undertaken beyond the pandemic phase based on emerging data and information.

As real-time data on vaccine stability are incrementally generated, there should be effective information exchange between the reference NRA or WHO, vaccine manufacturers and importing countries to ensure that updated shelf-lives are communicated in a timely manner to avoid the needless destruction of vaccines.

Transparency should be promoted through the publishing and sharing of regulatory information to facilitate information exchange among NRAs. In a pandemic or other public health emergency, it is particularly important that the reference NRAs and WHO publish their decisions and recommendations on authorized vaccines, and highlight any alerts.

6.1.1 Pathways for the review of post-authorization changes
Reliance pathways used for the initial authorization should also be applied to post-authorization changes as far as possible. Therefore, during a pandemic or other public health emergency, the NRAs of importing countries are encouraged to recognize or rely on the decisions of the reference NRA or on WHO recommendations for PQ/EUL with regard to post-authorization changes. Major or critical manufacturing process changes that impact the safety or use of a vaccine should be reported to the NRAs of importing countries.

If recognition of WHO EUL has been used for the initial authorization, the NRA of the importing country may want to refer to the terms of authorization as defined by the WHO EUL decision, if their national legal framework allows for such reference, to facilitate maintenance of the emergency use. This will allow for a prompt and appropriate response to any updates to the WHO EUL, such as new manufacturing sites, new indication, extension of shelf-life and so on.

6.1.1.1 Documentation required
If recognition or reliance is to be used:

- evidence of the reference NRA’s approval or WHO PQ/EUL recommendation of the post-approval change(s);
- unredacted assessment reports of the reference NRA or WHO PQ/EUL (as far as is possible); and
- documentation essentially the same as that submitted to the reference NRA or WHO PQ/EUL, as specified in published WHO guidance on GReLP (9).
If an independent review is to be conducted:

- full supporting documentation with the relevant quality, safety and efficacy data applicable to the proposed change(s) in accordance with national guidelines.

As highlighted above, reliance ranges from the full recognition of the decision of a reference NRA or trusted institution such as WHO (using minimum documentation) to the use of full unredacted assessment reports to make an independent decision. The extent of reliance to be applied, and documentation required, will be determined by countries in line with their national legal frameworks. In an emergency situation, an independent review should only be considered if recognition or reliance cannot be used.

6.2 Importation and market surveillance and control

6.2.1 Import authorization

Once authorization has been granted for a vaccine, countries should have a procedure in place for approving its importation within 5 working days from the date of receipt of the import authorization application. The WHO Guidelines on import procedures for medical products (10) provide guidance for NRAs, trade ministries, customs authorities, port authorities and importing agents on simplifying the checking and handling of vaccines for import. During importation, the vaccine is checked to verify compliance with the authorization, for example with regard to labelling. To protect vaccine recipients and ensure that no substandard or falsified products enter the country, it is vital that existing national legislation relating to importation covers all vaccines, including donations (32).

NRAs are encouraged to follow the principles outlined in WHO operational guidance on the legal and regulatory framework facilitating vaccine deployment (32).

Some NRAs with no or very limited capacity to conduct reviews for authorization may use the import permit as a form of authorization of the vaccine. Countries should ensure that such vaccines have been approved by a reference NRA or trusted institution such as WHO. This procedure should be clearly defined by the NRA in the importing country during the interpandemic phase, including applicable timelines to prevent delays in the importation of the vaccine.

6.2.1.1 Documentation required

As a prerequisite for border and customs clearance, the importing agency or agent should be equipped to furnish the customs authority with the following documentation in respect of each consignment:
■ documents issued by the NRA in the importing country attesting that the importer is duly authorized to import the vaccines and that the products are duly authorized to be marketed or permitted to be imported into the importing country;
■ a batch release certificate issued by the manufacturer;
■ a safety data sheet, where applicable;
■ a relevant invoice, bill or delivery slip for the batch, including the product name, batch number, quantity, and expiry or manufacture date;
■ lot/batch release certificate issued by the NRA in the country/territory of origin; and
■ any other documentation required by national or regional legislation for customs clearance.

The high demand for vaccines during a pandemic or other public health emergency, whether due to shortages or inaccessibility, may result in the circulation of substandard and falsified vaccines or unapproved vaccines in both the legal and illegal distribution channels. NRAs in importing countries are particularly encouraged to ensure that their market control systems can prevent and detect substandard and falsified vaccines, and that the appropriate response capabilities are in place, including information sharing and reporting to the WHO global surveillance and monitoring system which provides information on substandard and falsified medicines to countries. In addition, the principles set out in published WHO guidance on good storage and distribution practices for medical products should be followed to ensure that the integrity of vaccines is not compromised. Regardless of the lot release procedure applied, a record must also be kept of all lots received in the country to facilitate their traceability.

6.3 Pharmacovigilance
NRAs are encouraged to follow the procedures for post-authorization surveillance of adverse events as described in the national pandemic and emergency use vaccine deployment plan. This should follow the principles set out in the WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines, the WHO Global manual on surveillance of adverse events following immunization and internationally recognized guidelines on good pharmacovigilance practices – see for example. The national

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pharmacovigilance system should ensure that all stakeholders (including manufacturers, regulatory authorities, immunization programmes, vigilance centres and others) closely coordinate and share the information they require to meet their responsibilities.

A crisis management plan and RMP for pandemic or other emergency use vaccines should be developed and monitored by the manufacturer with input from the NRA and the national immunization programme (if needed) to enable continuous monitoring and management of the benefit–risk profile of the vaccine during marketing and use.

At the time of initial authorization, trials (including safety studies) may not have been conducted in special populations such as children, pregnant women, lactating women, immunocompromised individuals, people with pre-existing health conditions and other groups of interest (which may differ from country to country). Special consideration may therefore need to be given to the inclusion of post-authorization Phase IV studies by manufacturers in the RMP.

National systems for post-authorization surveillance, including the reporting of AEFI and causality assessment of serious adverse events, should not be compromised by the implementation of a pandemic or other emergency use vaccination campaign. NRAs are strongly urged to identify AEFI of interest as soon as they emerge and to use tools such as VigiFlow\(^{10}\) and VigiMobile\(^{11}\) to facilitate AEFI reporting and management.

NRAs should take timely regulatory action in relation to any safety issues identified post-authorization, including approval changes in the reference NRA country, some of which may require the communication of important risks to the public and other stakeholders through changes in the product information. NRAs should also actively engage with stakeholders (such as professional associations) to ensure the adequate and effective communication and minimization of any identified risks.

NRAs are encouraged to use reliance in pharmacovigilance – for example, by adapting existing warnings and precautions published by reference NRAs to the local context. These may appear in product information sheets, RMPs, direct health care professional communications (“dear doctor” letters) and patient information sheets. For this purpose, NRAs should closely monitor the information produced by reference NRAs and other sources.

The NRA, in collaboration with the local marketing authorization holder, should also plan and implement active surveillance studies, including pregnancy registries if resources are available.

\(^{10}\) For more information see: https://who-umc.org/pv-products/vigiflow/vaccine-safety-surveillance-in-vigiflow/.

\(^{11}\) For more information see: https://who-umc.org/pv-products/vigiflow/vigimobile/.
6.4 **Lot release**

NRAs should have the flexibility in their legal framework to waive requirements for independent testing in an emergency situation and to instead use recognition/reliance mechanisms. In a pandemic or other public health emergency, lot release and quality control of vaccines by the NRA and/or national control laboratories (NCLs) of importing countries should follow the guidance set out in relevant WHO documents (26, 35–38) and be completed within the shortest possible time.

Vaccines received by importing countries should be produced in compliance with GMP and tested for quality and safety by the vaccine manufacturer. Typically, such vaccines are also subjected to independent quality control testing and released by the producing country’s NRA/NCL in accordance with the WHO Guidelines for independent lot release of vaccines by regulatory authorities (26). Recognition of the lot release certificate of the NRA/NCL of the producing country is strongly recommended by WHO in accordance with national laws (26). For vaccines supplied through United Nations agencies, it is recommended that further release testing by the NRA/NCL of receiving countries should not be performed because such vaccines are prequalified or listed by WHO and released by the producing country’s NRA/NCL. For self-procured WHO PQ/EUL vaccines or vaccines approved by a reference NRA, it is not recommended that further release testing by the NRA/NCL of receiving countries be performed because such vaccines have been prequalified or listed by WHO and released by the producing country’s NRA/NCL.

For self-procured pandemic or other emergency use vaccines that do not have a WHO PQ/EUL recommendation and are not approved by a reference NRA, the NRA/NCL of the procuring country may, in the event of a pandemic or other public health emergency, conduct lot release through review of the summary lot protocol. Further laboratory testing by the NRA/NCL of the receiving country is normally not necessary, based on risk assessment.

The procedures adopted should ensure the deployment of vaccines without undue delay. Where NRA lot release has not been conducted for a pandemic or other emergency use vaccine (such as a vaccine approved using the emergency authorization procedure of the NRA of the producing country), importing countries with limited capacity or resources (including time) to conduct laboratory testing may rely on the batch release certificate issued by the quality control unit of the manufacturer. Some countries do not issue a lot release certificate even though the vaccine has been granted marketing authorization. In this scenario, the NRA/NCL of the producing country may be requested to produce a document to certify the quality of the batch and facilitate a summary lot protocol review. The model summary protocol may not be available on the WHO website for some vaccines and in such instances the manufacturer’s template should be used.
Appropriate and adequate supply chain procedures should be followed for all types of vaccines, including the capturing of lot distribution and critical lot information. Product monitoring becomes more important when the NRA of the importing country is not conducting quality testing through their NCL and is relying on the lot release of other NRAs.

Authors and acknowledgements

The first draft of these WHO Guidelines was prepared by a WHO drafting group comprising: Dr T. Sithole, consultant, Zimbabwe; Dr H. Meyer, Paul-Ehrlich-Institut, Germany; Dr O. Engelhardt, Medicines and Healthcare products Regulatory Agency, United Kingdom; Dr C. Young, Health Canada, Canada; Dr E. Nkansah, Food and Drugs Authority, Ghana; Dr P. Huleatt, Therapeutic Goods Administration, Australia; and Dr R. Ostad Ali Dehaghi, Dr A. Khadem Broojerdi and Dr D. Lei, World Health Organization, Switzerland, taking into consideration the outcomes and feedback from implementation workshops on the WHO Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries, as well the experience gained in regulatory requirements and challenges during the COVID-19 pandemic. Further discussion was held and consensus reached during a WHO drafting group meeting on the revision of the above Guidelines held virtually on 18–20 July 2022.

The second draft of the Guidelines (WHO/BS/2023.2453) was prepared by Dr T. Sithole, Dr H. Meyer, Dr O. Engelhardt and Dr E. Nkansah; and by Dr R. Siggers, Health Canada, Canada, Mr P. Akarapanon, Food and Drug Administration, Thailand and Dr O. Malik, Drug Regulatory Authority of Pakistan, Pakistan; and Dr R. Ostad Ali Dehaghi, Dr A. Khadem Broojerdi and Dr D. Lei, World Health Organization, Switzerland following a WHO informal consultation held in Istanbul, Türkiye on 17–19 April 2023 and attended by: Mr P. Akarapanon, Food and Drug Administration, Thailand; Ms S. Choden, Bhutan Food and Drug Authority, Bhutan; Dr H. El Saeed Mohamed Metwally Attia, Egyptian Drug Authority, Egypt; Dr O. Engelhardt, Medicines and Healthcare products Regulatory Agency, United Kingdom; Dr S. Hababbeh, Jordan Food and Drug Administration, Jordan; Dr A. Hacker, Coalition for Epidemic Preparedness Innovations, United Kingdom; Mrs L. Lan, Drug Administration of Viet Nam, Viet Nam; Dr O. Malik, Drug Regulatory Authority of Pakistan, Pakistan; Dr H. Meyer, Paul-Ehrlich-Institut, Germany; Dr N. Mirbek, Department of Medicines and Medical Devices, Kyrgyzstan; Dr P. Nkambule, South African Health Products Regulatory Authority, South Africa; Dr E. Nkansah, Ghana Food and Drugs Authority, Ghana; Dr D. Pascual, Centre de Control Estatal de Medicamentos Equipos y Dispositivos Médicos, Cuba; Ms V. Phanthavong, Food
and Drug Department, Lao People’s Democratic Republic; Dr D. Puspitasari, Food and Drug Administration, Indonesia; Dr R. Siggers, Health Canada, Canada; Dr T. Sithole, Medicines Control Authority of Zimbabwe, Zimbabwe; Ms U. Tandukarm, Ministry of Health and Population, Nepal; and Ms R.M. Vicentino, Food and Drug Administration, Philippines; and by Dr M. Ismail, WHO Regional Office for Africa; Ms A. Mata and Ms B. Segastuy, WHO Regional Office for the Americas/Pan American Health Organization; Dr A. Inoubli, WHO Regional Office for South-East Asia; Ms D. Pirgari, WHO Regional Office for Europe; Dr A.M. Al-Nuseirat, WHO Regional Office for the Eastern Mediterranean; and Dr G. Hill, WHO Regional Office for the Western Pacific; and by Dr A. Khadem Broojerd, Dr R. Ostad Ali Dehaghi, Dr D. Lei, Ms J. Barragan, Mrs M. Valentim and Ms E. Kim, World Health Organization, Switzerland.

Further changes were made to document WHO/BS/2023.2453 by the WHO Expert Committee on Biological Standardization. An editorial review of the resulting document was then completed by Dr T. Waddell, United Kingdom in accordance with WHO requirements for all documents appearing in the WHO Technical Report Series.

References


Annex 3

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 hybrid-format meeting held on 16–19 October 2023, 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 the table below should be used in accordance with its instructions for use (IFU).

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### Additions\(^{13}\)

<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>Alpha-fetoprotein (human)</td>
<td>7800 IU/ampoule</td>
<td>Second WHO International Standard</td>
</tr>
<tr>
<td>Follicle-stimulating hormone and luteinizing hormone for bioassay (human, urinary)</td>
<td>177 IU/ampoule FSH  170 IU/ampoule LH</td>
<td>Sixth WHO International Standard</td>
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<tr>
<td>Thyroid-stimulating hormone (human, pituitary)</td>
<td>11.7 mIU/ampoule</td>
<td>Fourth WHO International Standard</td>
</tr>
<tr>
<td><strong>Blood products and related substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombin activatable fibrinolysis inhibitor (plasma)</td>
<td>Activity: 0.87 IU/ampoule Antigen: 0.92 IU/ampoule Antigen: 7.43 μg/ampoule (expanded uncertainty limits = 7.05–7.82 with k=2 taken to correspond to a 95% level of confidence)</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td><strong>In vitro diagnostics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein S (plasma)</td>
<td>0.71 IU/ampoule activity  0.83 IU/ampoule free antigen  0.88 IU/ampoule total antigen</td>
<td>Third WHO International Standard</td>
</tr>
<tr>
<td>Q fever (Coxiella burnetii) antibodies (human, plasma)</td>
<td>100 U/ampoule for Phase I antigens  16 U/ampoule for Phase II antigens</td>
<td>WHO International Reference Reagent</td>
</tr>
<tr>
<td><strong>Standards for use in high-throughput sequencing technologies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gut microbiome DNA extraction (whole cell)</td>
<td>No unitage assigned</td>
<td>WHO International Reference Reagent</td>
</tr>
</tbody>
</table>

\(^{13}\) Unless otherwise indicated, all materials are held and distributed by the Medicines and Healthcare products Regulatory Agency, Potters Bar, Herts, EN6 3QG, United Kingdom.
<table>
<thead>
<tr>
<th>Material</th>
<th>Unitage</th>
<th>Status</th>
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<tbody>
<tr>
<td><strong>Standards for use in public health emergencies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 RNA for NAT-based assays</td>
<td>7.50 log₁₀ IU/ampoule</td>
<td>Second WHO International Standard</td>
</tr>
<tr>
<td><strong>Vaccines and related substances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nipah virus antibodies for neutralization assays (human, serum)</td>
<td>250 IU/ampoule</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Nipah virus antibodies for binding assays (human, serum)</td>
<td>250 IU/ampoule anti-glycoprotein IgG</td>
<td>First WHO International Standard</td>
</tr>
<tr>
<td>Ross River virus antibodies for neutralization assays (human, plasma) ¹⁴</td>
<td>500 U/vial</td>
<td>WHO International Reference Reagent</td>
</tr>
</tbody>
</table>

¹⁴ Held and distributed by the Paul-Ehrlich-Institut, Paul-Ehrlich-Str. 51–59, 63225 Langen, Germany (https://www.pei.de/EN/home/home-node.html).
SELECTED WHO PUBLICATIONS OF RELATED INTEREST

**WHO Expert Committee on Biological Standardization**
Seventy-seventh report.
WHO Technical Report Series, 1048, 2023 (xiv + 137 pages)

**WHO Expert Committee on Biological Standardization**
Seventy-sixth report.
WHO Technical Report Series, 1045, 2023 (xvi + 330 pages)

**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**
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)

Website: https://www.who.int/health-topics/Biologicals#tab=tab_1

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WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland;
email: bookorders@who.int; order online: www.who.int/bookorders
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 in hybrid format in October 2023. 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 WHO document entitled Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries was adopted.

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; in vitro diagnostics; standards for use in high-throughput sequencing technologies; 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 WHO document adopted on the advice of the Committee is then presented as part of this report (Annex 2). Finally, all new and replacement WHO international reference standards for biological products established during the October 2023 meeting are summarized in Annex 3. 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.