Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 19 to 23 October 2020

The 72nd meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held from 19 October to 23 October 2020 by WebEx due to the restrictions imposed during the COVID-19 pandemic. After its extraordinary meeting in August 2020, held primarily to address urgent COVID-19 issues, the ECBS focused during the current meeting on a wider range of biological standardization matters, in addition to a number of ongoing issues in relation to the pandemic. ECBS members, regulatory authority representatives and subject matter experts from governmental organizations participated in the meeting from Monday 19 October to Thursday 22 October 2020. An open information-sharing session involving all participants, including non-state actors, was held on Monday 19 October. All decisions and recommendations regarding the adoption of written standards and establishment of measurement standards were made in a closed session held on Friday 23 October attended only by ECBS members and WHO staff. The ECBS also provided advice to WHO on a number of strategic issues. A full report of the meeting will be published in the WHO Technical Report Series in 2021.

The main outcomes of the 72nd ECBS meeting are summarized below:

Three WHO written standards were recommended for adoption; two supporting the production and regulatory evaluation of vaccines and the third providing guidance on the accelerated national assessment and registration of WHO-prequalified in vitro diagnostics (IVDs):

1. **Recommendations to assure the quality, safety and efficacy of typhoid conjugate vaccines**

   Typhoid fever continues to be endemic in many low- and middle-income countries, particularly where access to safe water and basic sanitation is limited. Estimates of global disease burden range from 11 to 21 million cases and 145 000 to 161 000 deaths annually. Vaccines based on the Vi polysaccharide antigen have been available for several decades but have the same limitations as other polysaccharide vaccines in that they are poorly immunogenic in the young, confer short-lived immunity and cannot be boosted. Typhoid conjugate vaccines (TCVs) were developed to overcome these shortcomings and WHO guidelines on their quality, safety and efficacy were adopted in 2013. As several TCVs have now been licensed and more are in development, this revised document provides recommendations for their evaluation rather than the previous guiding principles. Other important developments reflected in the updated text include the establishment of Vi antigen and antibody measurement standards by the ECBS, publication of a WHO Strategic Advisory Group of Experts position paper on the use of TCVs, approval of funding for TCV introduction in Gavi-eligible countries and the WHO prequalification of Typbar-TCV in 2017.

2. **Recommendations to assure the quality, safety and efficacy of enterovirus 71 vaccines (inactivated)**

   Enterovirus 71 (EV71) is associated with hand, foot and mouth disease (HFMD) throughout the world and has caused epidemics in Asia, Europe and North America. Manifestations of the disease range from asymptomatic infection to mild HFMD to neurological disease with severe central nervous system complications and cardiopulmonary failure. In severe cases mortality rates can be high, especially in children

aged 5 years and younger. Several EV71 vaccines are now being developed, with three inactivated vaccines approved in China. These new recommendations take into account existing WHO guidance on the evaluation of similar vaccines (such as inactivated poliomyelitis vaccines and hepatitis A vaccines) and refer to recently established antiserum and vaccine standards. The document provides recommendations to regulators, vaccine developers and manufacturers on the research, evaluation, manufacture and quality control of inactivated EV71 whole virus vaccines.

3. **Collaborative procedure between WHO and NRAs in the assessment and accelerated national registration of WHO-prequalified IVDs**

The assessment of applications for the approval and registration of IVDs by national regulatory authorities (NRAs) is an essential step in ensuring their quality, safety and performance before they come to market. The collaborative registration procedure (CRP) provides a pragmatic approach for accelerating national assessment and registration of WHO-prequalified IVDs by taking into consideration the WHO prequalification dossier assessment, performance evaluation, and manufacturing site inspection reports. Key CRP principles include: (a) the voluntary participation of NRAs and manufacturers; (b) sharing of confidential information between WHO and participating NRAs; (c) assessment and registration of the same product as prequalified by WHO; and (d) monitoring of product status by both the NRA and WHO. This procedure will benefit all parties. NRAs will have access to WHO prequalification reports to support their decision-making and save internal resources. The burden on manufacturers will also be reduced as the information submitted to NRAs will be similar to that already submitted to WHO during prequalification, and the registration timeline will be faster (within 90 days) and more predictable. In addition, WHO will receive feedback on WHO prequalification outcomes allowing for improvement of its processes, while the timely availability of IVDs will result in quicker access by health care workers and patients.

As shown in Table 1, the ECBS also established 12 new WHO international reference materials and three replacement WHO international reference materials. The ECBS also endorsed 13 proposals for future new or replacement international reference materials.

Table 1
WHO international reference materials established by the ECBS in October 2020

Material	Unitage	Status
Biotherapeutics other than blood products		
Interferon alpha 2b	24 000 IU/ampoule	Third WHO International Standard
Bevacizumab	1000 IU/ampoule for VEGF neutralizing activity; 1000 IU/ampoule for VEGF binding activity	First WHO International Standard
Insulin-like growth factor-I (recombinant, human)	33.0 µg/ampoule (expanded uncertainty = 30.5–35.6 µg/ampoule; k = 2.36)	Second WHO International Standard

Chorionic gonadotrophin (human)	159 IU/ampoule for bioassay; 186 IU/ampoule for immunoassay: corresponding to 0.41 nmol/ampoule (expanded uncertainty 0.40-0.43 nmol/ampoule; k = 2.12)	Sixth WHO International Standard
Blood products and related substances		
Anti-human platelet antigen-15b immunoglobulin G (human)	[No assigned unit] Detection at 1 in 8 dilution validates assay	WHO International Reference Reagent
In vitro diagnostics		
Herpes simplex virus type 1 DNA for NAT-based assays	7.19 $\log_{10}$ IU/vial	First WHO International Standard
Herpes simplex virus type 2 DNA for NAT-based assays	7.31 $\log_{10}$ IU/vial	First WHO International Standard
West Nile virus lineage 1 RNA for NAT-based assays	7.20 $\log_{10}$ IU/vial	First WHO International Standard
West Nile virus lineage 2 RNA for NAT-based assays	[No assigned unit]	WHO International Reference Reagent
Standards for use in high-throughput sequencing technologies		
Porcine circovirus type 1 (CBER code: SC-VR-6000P)	2.7 x 10^{11} genome copies/mL	WHO International Reference Reagent
Mammalian orthoreovirus type 1 (CBER code: SC-VR-6001P)	1.4 x 10^{10} genome copies/mL	WHO International Reference Reagent
Feline leukaemia virus (CBER code: SC-VR-6002P)	5.3 x 10^{10} genome copies/mL	WHO International Reference Reagent
Human respiratory syncytial virus (CBER code: SC-VR-6003P)	1.0 x 10^{9} genome copies/mL	WHO International Reference Reagent
Epstein-Barr virus (CBER code: SC-VR-6004P)	3.7 x 10^{8} genome copies/mL	WHO International Reference Reagent
Vaccines and related substances		
Anti-MERS-CoV immunoglobulin G (human)	250 IU/ampoule	First WHO International Standard

In addition to the adoption of the written standards and establishment of international reference materials shown above, the ECBS also discussed the following:

1. Numerous monoclonal antibodies (mAbs) for treating and preventing infectious diseases are now in development. Because of their relatively short development time, rapid onset of effect and history of safe use, the development of mAbs as potential therapeutics for COVID-19 is a high priority and such products are likely to become available sooner than vaccines. Since 2013, a range of WHO guidance documents on mAbs has been published focusing primarily on their use as biotherapeutics for noncommunicable diseases. Comprehensive guidance on the development of mAbs against COVID-19 and other infectious diseases, and on their clinical evaluation, is now urgently needed. The ECBS endorsed the proposal to develop WHO guidance broadly applicable to all mAbs intended for use against infectious diseases, with disease-specific "special considerations" supplements to be drafted as required.

2. COVID-19 convalescent plasma (CCP) and hyperimmune immunoglobulin have the potential to reduce mortality in COVID-19 patients and are currently being investigated as potential therapies. The ECBS was updated on WHO activities in this area and expressed its support for the development and dissemination of interim WHO guidance on the safe collection of CCP. It noted that WHO collaboration with the International Society of Blood Transfusion had improved the availability of protocols for clinical studies involving CCP and that WHO had communicated to key stakeholders the pressing need for an anti-SARS-CoV-2 antibody standard for calibrating CCP potency in International Units. A proposal to develop a WHO international standard for this purpose had been endorsed by the ECBS in August 2020, with establishment expected to occur in December 2020.

3. The ECBS was updated on the development of a WHO guidance document on the centralization of blood donation testing and processing, and of a WHO white paper on increasing access to plasma-derived medicinal products (PDMPs) in low- and middle-income countries. These documents are closely aligned with resolutions WHA58.13 and WHA63.12 on the provision of safe blood and blood components (including PDMPs) and support the WHO Action framework to advance universal access to safe, effective and quality assured blood products 2020–2023. The ECBS noted the benefits of centralized blood donation testing for national blood systems, including the enhanced management of emergency situations (such as the current pandemic) that affect blood supply and safety. The development of these much needed documents highlighted the need to prioritize the revision of several related WHO guidance documents.

4. The ECBS reviewed its recent activities with regard to the ongoing COVID-19 pandemic and concluded that there were no gaps at present. WHO measurement standards for molecular diagnostics and for antigen and antibody assays were being developed at an unprecedented rate and it was anticipated that these standards would be established at the next meeting of the ECBS in December 2020. In most cases, interim working reagents had already been made available to support research and development. WHO had already published guidance documents relevant to the development of therapeutic antibodies, vaccines and CCP, and the WHO Guidelines on the quality, safety and efficacy of plasmid DNA vaccines had been adopted at the previous meeting of the ECBS. Proposals to develop WHO guidance documents on: (a) regulatory considerations for the evaluation of messenger RNA (mRNA) vaccines; and (b) the evaluation of mAbs for prophylaxis or treatment of infectious diseases (see above) had now been endorsed, with specific guidance to be provided on COVID-19 mRNA vaccines and mAb therapeutics. In addition, a Working Group had been established to investigate potential factors underlying the genetic instability of SARS-CoV-2 viruses during propagation in different mammalian cell lines. Although this issue is not currently regarded as part of biological standardization activities,

it may impact on future WHO guidance on the production and evaluation of COVID-19 vaccines and other biological products.

The next meeting of the ECBS is scheduled for 9-10 December 2020.