Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 18 to 22 October 2021

The 74th meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held from 18 October to 22 October 2021 by video conference due to travel restrictions resulting from the COVID-19 pandemic. In addition to its ongoing work to address urgent needs arising from the current pandemic, the ECBS also focused on a wide range of biological standardization issues. ECBS members, regulatory authority representatives and subject matter experts participated in the meeting from Monday 18 October to Thursday 21 October 2021. An open information-sharing session involving all participants, including non-state actors, was held on Monday 18 October 2021. All ECBS decisions and recommendations regarding the adoption of WHO written standards and the establishment of WHO measurement standards were made during a closed session held on Friday 22 October attended only by ECBS members and WHO staff. The ECBS also provided advice and recommendations to WHO on a number of key strategic issues. A full meeting report will be published in the WHO Technical Report Series in 2022.

The main meeting outcomes included the recommended adoption of the following two WHO written standards:

- **Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations**

  The unprecedented rapid development and clinical evaluation of messenger RNA (mRNA) vaccines in response to the COVID-19 pandemic has highlighted the urgent need for WHO guidance on evaluating the quality, safety and efficacy of such vaccines. The speed with which candidate mRNA vaccines can be developed makes the technology eminently suited to the development of vaccines against emerging pathogens during public health emergencies such as the COVID-19 pandemic. Recent advances in the manufacturing and stabilization of mRNA have established the approach as an important vaccine technology. In order to set out the principles for the anticipated licensure of COVID-19 and other mRNA vaccines this WHO regulatory considerations document was developed and adopted on the advice of the ECBS. The scope of the document covers the manufacture, quality control, and nonclinical and clinical evaluation of mRNA vaccines intended for the prevention of infectious diseases in humans.

- **Amendment to the WHO Recommendations to assure the quality, safety and efficacy of live attenuated yellow fever vaccines**

  Highly effective live attenuated yellow fever vaccines have been in use since the late 1930s and a wealth of data is available on their safety. However, rare serious adverse reactions associated with their use include neurological and viscerotropic disease. It is therefore crucially important to assess the levels of neurotropism and viscerotropism exhibited by new virus master or working seeds compared to those exhibited by vaccines shown to be clinically safe. Appendix 2 of the current WHO Recommendations to assure the quality,

safety and efficacy of live attenuated yellow fever vaccines sets out how virus master and working seed lots should be tested in non-human primates. Following observed discrepancies in clinical scoring during the assessment of working seed lots in non-human primates, a request was made to WHO to amend the current guidance. The ECBS concurred with this request and recommended the adoption of the correspondingly amended Appendix 2.

As shown in Table 1, the ECBS also established five new WHO international reference materials and four replacement WHO international reference materials. The ECBS also endorsed 10 proposals for future new or replacement international reference materials.

Table 1
WHO international reference materials established by the ECBS in October 2021

Material	Unitage	Status
Biotherapeutics other than blood products		
Follicle-stimulating hormone (human, recombinant) for bioassay	137 IU/ampoule	Third WHO International Standard
Blood products and related substances		
von Willebrand factor concentrate	VWF:Ag 12.0 IU/ampoule VWF:RCo 8.7 IU/ampoule VWF:CB 9.8 IU/ampoule VWF:GPIbR 8.6 IU/ampoule VWF:GPIbM 7.3 IU/ampoule	Third WHO International Standard
Ferritin (human, recombinant)	10.5 µg/ampoule Expanded uncertainty limits = 10.2–10.8 µg/ampoule (95% confidence; k = 2.23)	Fourth WHO International Standard
In vitro diagnostics		
Mycobacterium tuberculosis (H37Rv) DNA for NAT-based assays	6.3 $\log_{10}$ IU/vial	First WHO International Standard
Varicella zoster virus DNA for NAT-based assays	7.0 $\log_{10}$ IU/vial	First WHO International Standard
Anti-Lassa fever virus antibodies	25 IU/ampoule for neutralizing antibody 250 IU/ampoule for anti-GP binding IgG 250 IU/ampoule for anti-NP binding IgG	First WHO International Standard
Anti-Lassa fever virus antibodies	[No unitage assigned]	First WHO International Reference Panel
Anti-thyroid peroxidase antibodies	555 IU/ampoule	First WHO International Standard
Vaccines and related substances		

Diphtheria antitoxin equine	57 IU/ampoule	Second WHO International Standard

In addition to recommending the adoption of the two written standards and the establishment of the nine reference preparations shown above, the ECBS also discussed the following:

1. The ECBS was updated on WHO COVID-19 activities in the context of the three pillars of the WHO Access to COVID-19 Tools (ACT) Accelerator initiative. With regard to the therapeutic pillar, two WHO guidance documents on monoclonal antibodies were now being developed. The first of these focuses on manufacturing aspects and was currently the subject of public consultation, while the second will focus on the nonclinical and clinical evaluation of monoclonal antibodies used against infectious diseases. With regard to the ACT Accelerator vaccine pillar (COVAX) the adoption of the mRNA vaccines document described above will be followed by the finalization of a manual on the development of secondary antibody standards – of crucial importance in meeting the demands arising from the clinical evaluation of COVID-19 vaccines. This resource will form part of focused WHO technical support to the users of WHO standards including through the conducting of webinars on their intended use. Efforts are also under way to further inform and support the scientific and regulatory community with respect to the need to express neutralization assay results from clinical trials in IU as a common yardstick in efforts to define correlates of protection. Support to the diagnostic pillar of the ACT Accelerator is being provided through the ongoing development of the SARS-CoV-2 antigen standard for rapid diagnostic testing that was endorsed by the ECBS in December 2020. A collaborative study will be conducted in late 2021 and early 2022 with the aim of submitting a proposal to the ECBS for the establishment of the antigen standard in 2022.

2. With regard to other upcoming measurement standards relevant to the COVID-19 response, the ECBS was informed that unprecedented demand for the recently established First WHO International Standard for anti-SARS-CoV-2 immunoglobulin had resulted in its rapid depletion. The ECBS endorsed a proposal to develop a replacement standard while recognizing the challenge of sourcing a suitable replacement material. The ECBS also endorsed a further proposal to develop a panel of reference sera specific for SARS-CoV-2 variants of concern that could be expanded should new variants emerge. The panel will facilitate development of the essential serological assays needed to study the impact of new variants on the efficacy of existing vaccines and therapeutics.

3. There is currently little evidence to support the use of COVID-19 convalescent plasma in the treatment of moderate to severe COVID-19, and uncertainty exists regarding its potential utility in treating mild or asymptomatic COVID-19 infection. The ECBS was presented with the conclusions of a recently published Cochrane living systematic review and noted that this was a developing field with many studies still ongoing and firm conclusions on the efficacy of this approach in different subgroups of patients yet to be reached.

4. A newly established WHO Advisory Group on Blood Regulation, Availability and Safety (AG-BRAS) was formed in response to the need of WHO for wide-ranging guidance from experts both in blood regulation and transfusion medicine. The establishment of the new advisory group reflects the need for suitable diversity of expertise and experience, and for balanced representation from all six WHO regions, to support delivery of the WHO Action framework to advance universal access to safe, effective and quality-assured blood

products 2020–2023. The ECBS acknowledged the many contributions made over the years by the Blood Regulators Network (BRN) in strengthening harmonization and standards in blood product safety and quality, and noted that the role of the BRN would now be assumed by AG-BRAS going forward. The ECBS expressed its support for the new advisory group and anticipated its furthering of progress in this area.

5. The ECBS was updated on the development of a white paper setting out a regulatory framework for cellular, tissue and gene therapies. The principal objective of the white paper would be to develop a common language and risk-based classification for these highly complex products, including the subset of these products commonly referred to as advanced therapy medicinal products. The white paper is expected to facilitate regulatory convergence and stimulate dialogue between countries on appropriate measures to improve worldwide access to these products. A first round of public consultation in late 2021 would provide an opportunity for all stakeholders to comment on the proposed document. The ECBS expressed its strong support for the development of the white paper and further noted that this once again highlighted the inevitable proliferation of these increasingly complex and challenging products – several of which have already come before ECBS for its consideration. Without additional specialized expertise in this area providing WHO with fully informed guidance in this field will present a significant challenge. WHO was therefore urged to consider expanding the expertise of the ECBS and of its own biologicals team to provide the specialist knowledge needed to address the formidable regulatory and other challenges associated with this complex class of biological product.

6. The ECBS expressed its concern with regard to potential upcoming changes to the United Kingdom's National Institute for Biological Standards and Control (NIBSC). NIBSC is the foremost WHO collaborating centre in the development of WHO international reference materials for biological products and its activities are pivotal not only to the work of the ECBS but to the advancement of regulatory science worldwide. In addition, the role played by NIBSC in developing and distributing WHO international reference materials is vital in ensuring the national licensing and release of a huge range of much-needed diagnostics, vaccines, biotherapeutics and other biological products. Without the contribution made by NIBSC the hard won gains in improving access to vital medicines in some of the poorest countries in the world will be jeopardized and the prospect of achieving many of the goals and targets of internationally agreed initiatives such as the sustainable development goals will be materially damaged. The Committee strongly agreed with a proposal that WHO send as matter of urgency a letter to the appropriate national decision-making body in the UK setting out in the clearest possible terms the paramount importance of the work of NIBSC in achieving the global health aspirations of the international community.

The next meetings of the ECBS are scheduled for 4–8 April and 24–28 October 2022.