

Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held on 9 and 10 December 2020

The 73rd meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held on 9 and 10 December 2020 by Zoom video conferencing due to the restrictions imposed during the COVID-19 pandemic. Following its annual October meeting, this second exceptional meeting in 2020 focused on addressing a number of urgent biological standardization issues related to COVID-19. ECBS members, regulatory authority representatives and subject matter experts from governmental organizations participated in the first three sessions of the meeting. The first of these sessions was an open information-sharing session involving all participants, including non-state actors. All decisions and recommendations regarding the establishment of measurement standards were made in a closed session attended only by ECBS members and WHO staff. A full report of the meeting will be published in the WHO Technical Report Series in 2021.

The main outcomes of the 73rd ECBS meeting are summarized below:

The ECBS was updated on the progress made in the development of the following four new or revised WHO written standards:

1. Monoclonal antibodies for the prevention and treatment of infectious diseases: regulatory considerations

A number of monoclonal antibody (mAb) products are now being used to prevent and treat infectious diseases, with many more currently in clinical development. Due to their short development time, rapid impact and safety, the potential use of mAbs as therapeutics for COVID-19 is considered a high priority. However, existing WHO guidance on mAbs largely focuses on therapeutic products for noncommunicable diseases. Despite commonalities in manufacturing strategies for recombinant mAbs regardless of intended use, the current guidance offers little advice on preclinical and clinical evaluation specific to the use of mAbs for infectious disease prophylaxis or treatment. At its 72nd meeting held in October 2020, the ECBS had expressed its support for a proposal to develop a WHO regulatory considerations document specifically for mAbs used against infectious diseases in order to both clarify the application of existing relevant WHO guidance and to highlight additional new technological or clinical requirements. Having been updated on the progress made and feedback received to date, the ECBS reiterated its support for the continuation of this work. It was envisaged that the general regulatory considerations covered would be supplemented with current information on the development of mAbs for use against specific infectious disease pathogens such as SARS-CoV-2 and respiratory syncytial virus. The ECBS further recognized the need for significant updating of current WHO guidance in this area and expressed its support for a proposal to develop separate WHO guidelines on the manufacturing and quality assurance of mAbs regardless of clinical application.

2. Messenger RNA vaccines: regulatory considerations

Novel RNA-based vaccine platform technologies offer the potential to quickly develop vaccines against priority pathogens during public health emergencies. Recently, this potential has been realized during the COVID-19 pandemic, with messenger RNA (mRNA) vaccines entering clinical trials and in some countries receiving emergency use authorization. At its 71st meeting in August 2020, the ECBS had expressed its support

for the development of a WHO guidance document on regulatory considerations in the evaluation of mRNA vaccines. A pre-draft version had now been circulated among a working group of experts drawn from academia, industry, regulatory agencies and other stakeholders. In November 2020, the drafting group had met to discuss the feedback received and the further development of the document, with the aim of submitting a version for review by the ECBS in October 2021. Following a request for its advice on a number of issues, the ECBS indicated that the guidance should focus on mRNA vaccines intended for the prevention of infectious diseases, and should include self-amplifying RNA vaccines but not RNA-expressed mAbs. It further recommended that the document should provide guidance on specific aspects of quality, such as RNA integrity, characterization of the mRNA (including the level of capping and polyadenylation) and lipid encapsulation. Guidance on the in vitro assessment of vaccine potency would also be required. Given that the guidance was being developed in the context of the current COVID-19 pandemic, specific issues identified and experience gained during the development of SARS-CoV-2 mRNA vaccines should be incorporated and should be based, where possible, on published scientific evidence.

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

The current WHO Recommendations to assure the quality, safety and efficacy of live attenuated yellow fever vaccines were adopted in 2010. This document recommends that virus master and working seed lots should be tested for viscerotropism, immunogenicity and neurotropism in monkeys. Following reported discrepancies in the clinical scoring of monkeys during assessment of working seed lots, one manufacturer had requested that the neurotropism assessment be aligned with that used during neurovirulence testing of oral poliomyelitis vaccine seed lots. In this approach, clinical signs are recorded but do not form part of the assessment or pass/fail criteria. At its 71st meeting in August 2020, the ECBS had agreed that the Recommendations should be amended, and was updated on progress. Following a survey of yellow fever vaccine manufacturers and NRAs, a number of issues had emerged, including the use of different virus sub-strains for vaccine manufacture, technical challenges associated with neurovirulence testing in monkeys, the use of different reference viruses and the prospect of yellow fever vaccine development based upon the use of new cell substrates. It was anticipated that work on the amended document would commence in early 2021 and following public consultation would be presented to the ECBS for its review in October 2021.

4. Revision of the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs)

It is anticipated that the increasing availability of SBPs worldwide will increase competition between manufacturers, thus bringing down prices and improving access to such medicines. In line with World Health Assembly resolution WHA67.21 on access to biotherapeutic products, the ECBS at its 72nd meeting had recommended that a review be undertaken of current scientific evidence and experience in this field to inform the prospective revision of the 2009 WHO Guidelines on evaluation of similar biotherapeutic products (SBPs). This review had now been completed taking into account a number of national and regional guidelines, and a number of sections in the current WHO Guidelines had been identified for potential updating and revision. It is intended that the revision of the WHO Guidelines will lead to greater flexibility and reduced regulatory burden, while continuing to ensure the quality, safety and efficacy of

SBPs. Specific proposals for the revision of the quality, nonclinical and clinical sections of the WHO Guidelines were presented to the ECBS for information and advice.

As shown in Table 1, the ECBS also established four new WHO international reference materials. In addition, it endorsed a proposal to develop a standard for SARS-CoV-2 antigens to support the development, assessment and comparability of antigen-based rapid diagnostic tests.

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

Material	Unitage	Status
Biotherapeutics other than blood products		
Trastuzumab	1000 IU/ampoule (IOP activity) 1000 IU/ampoule (ADCC activity) 1000 IU/ampoule (HER2 binding activity) 1000 IU/ampoule (FcγRIIIa binding activity) 1000 IU/ampoule (ADCP)	First WHO International Standard
Standards for use in public health emergencies		
SARS-CoV-2 RNA for NAT-based assays	7.40 log ₁₀ IU/ampoule	First WHO International Standard
Anti-SARS-CoV-2 immunoglobulin	250 IU/ampoule (neutralizing antibody activity)	First WHO International Standard
Anti-SARS-CoV-2 immunoglobulin panel	[no assigned units]	First WHO International Reference Panel

The ECBS noted that the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin intended for use in neutralizing antibody assays had also been shown to reduce inter-laboratory variation when used in antigen-specific antibody binding assays, thus raising the possibility of its utility in the harmonization of such assays. The ECBS requested that further statistical analysis be conducted to confirm the suitability of the material for this purpose with a view to recommending the assignment of a unitage for antibody binding activity at its next meeting. However, in view of the urgent need for such a standard during the ongoing COVID-19 pandemic, the ECBS recommended that the material be made available immediately via the custodian laboratory on an interim basis as an internal reference reagent for the harmonization of antibody binding assays. Supporting data will be provided in the instructions for use, along with webinar-based and other technical assistance to ensure the correct use of the material.

In addition to reviewing the progress made in the development of the above-mentioned WHO written standards and establishing the international reference materials shown in Table 1 the ECBS also discussed the following:

1. A number of issues have been identified regarding the adoption and implementation of WHO international standards. Users of such standards were often unclear on how best to calibrate their assays and on the appropriate use of international units (IU). The effectiveness of webinars and face-to-face meetings for promoting standards and providing training was highlighted. A number of potential opportunities and approaches for promoting the correct use of COVID-19 standards in the coming months were discussed in light of the likely high initial level of demand for such standards.
2. The ECBS expressed its support for a proposal to update the WHO interim guidance on maintaining a safe and adequate blood supply during the COVID-19 pandemic and on the collection of convalescent plasma. In particular, updated guidance was now required on the temporary deferral of donors following vaccination against SARS-CoV-2. The updated guidance would also incorporate the latest information on the First WHO International Standard for anti-SARs-CoV-2 immunoglobulin recommended for establishment at the current meeting and would take into account the latest scientific evidence on the clinical use of convalescent plasma to treat SARS-CoV-2 infection.
3. An overview was provided of two draft documents prepared by the WHO Secretariat on the procedural aspects of WHO biological standardization activities in relation to the work of the ECBS. The first of these documents was intended for internal use by WHO and the second for public dissemination on the WHO website. Ensuring the public availability of the second document would serve to strengthen transparency among all stakeholders with regard to the ways in which WHO written and measurement standards were prioritized, developed and put forward for consideration by the ECBS. Specific issues to be addressed include the need to increase awareness of the mechanisms for receiving stakeholder inputs and to improve reporting of the status of the written and measurement standards pipelines. In their capacity as members of WHO expert advisory panels, individual ECBS members would be invited to review and comment upon both texts during their development.