Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 24 to 28 August 2020

The 71st meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held from 24 August to 28 August 2020 by WebEx due to the restrictions imposed during the COVID-19 pandemic. This exceptional session was held in addition to the annual October meeting of the ECBS and an emphasis was placed on addressing a number of urgent biological standardization issues relating to COVID-19. ECBS members, regulatory authority representatives and subject matter experts from governmental organizations participated in the meeting from Monday 24 August to Thursday 27 August. An open information-sharing session involving all participants, including non-state participants, was held on Monday 24 August. All decisions and recommendations regarding the adoption of written standards and the establishment of measurement standards were made in a closed session held on Friday 28 August attended only by ECBS members and WHO staff. In addition, the ECBS 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 71st ECBS meeting are summarized below:

Two WHO written standards to support the regulatory evaluation of vaccines were adopted:

1. **Guidelines for assuring the quality, safety and efficacy of plasmid DNA vaccines**

   Vaccines based upon the direct introduction of plasmid DNA encoding an immunogen into a vaccine recipient (known as plasmid DNA vaccines or DNA vaccines) are at an advanced stage of clinical development. Given the potential of this platform technology to address priority pathogens in public health emergencies and the pressing need for vaccine candidates to address the current COVID-19 pandemic, the availability of an up-to-date WHO written standard to drive international regulatory convergence for such vaccines is a matter of urgency. Since the adoption by the ECBS of the WHO Guidelines for assuring the quality and nonclinical safety evaluation of DNA vaccines in 2005 significant experience has been gained in their manufacture and control. This revised document sets out the guiding principles for evaluating the quality, safety and efficacy of plasmid DNA vaccines for human use. The revision also addresses several issues specifically associated with DNA vaccines, including the need to consider the impact of the delivery device on vaccine efficacy, the role of DNA vaccines in priming an immune response as part of a prime-boost vaccination strategy and the challenge of assessing vaccine potency in the laboratory.

2. **Guidelines for the safe production and quality control of poliomyelitis vaccines**

   At its 69th meeting in 2018, the ECBS adopted the WHO Guidelines for the safe production and quality control of poliomyelitis vaccines. These Guidelines incorporated biosafety measures consistent with GAPIII requirements, including several relating to the physical design of facilities and to quality control testing that were added after the final round of public consultation. Following publication of the Guidelines, poliomyelitis vaccine manufacturers requested that WHO consider the use of more flexible facility-specific risk-based approaches. In consultation with the Containment Advisory Group, the ECBS at its 70th meeting had recommended the amendment of the Guidelines in the three specific areas of: (a) the requirement for showering when exiting the containment facility; (b) allowing the use of non-dedicated quality control laboratories; and (c) permitting the removal of

certain samples for testing outside the containment facility. Following detailed discussion of the interpretation and implications of the amended text for vaccine manufacturers, the proposed amendments were adopted.

As shown in Table 1, the ECBS also established two new WHO international reference preparations and one replacement WHO international reference preparation. In addition, the ECBS endorsed four proposals for future new or replacement preparations.

Table 1
WHO International Standards and Reference Reagents established by the ECBS in August 2020

Preparation[1]	**Unitage**	**Status**
Blood products and related substances		
Thrombin	90 IU/ampoule	Third WHO International Standard
In vitro diagnostics		
Plasmodium vivax antigen	1000 IU/ampoule	First WHO International Standard
Vaccines and related substances		
Anti-malaria (*Plasmodium vivax*) human plasma	100 U/ampoule	First WHO Reference Reagent

In addition to the adoption of written standards and establishment of reference preparations, the ECBS also discussed the following:

1. The ECBS was briefed on the impact of COVID-19 on the work of WHO on vaccines and biological therapeutic medicines. WHO has set out the guiding principles for COVID-19 vaccine standardization on its website, explaining how current WHO written standards provide useful guidance and information on the development, production and evaluation of candidate COVID-19 vaccines, together with information on the current status of measurement standards projects. It is clear, however, that additional written and measurement standards specific to COVID-19 are required.

2. Although no RNA-based vaccines have yet been approved for human use, this platform technology has the potential to facilitate the rapid development of vaccines against priority pathogens in public health emergencies. Notably, RNA vaccines were among the first candidates to enter clinical development during the current COVID-19 pandemic, prompting requests for regulatory guidance. Because of significant differences in the way RNA vaccines are produced and evaluated, it was considered inappropriate to incorporate such guidance into the revised WHO plasmid DNA vaccines Guidelines adopted at the current meeting. The ECBS instead supported the development of a separate document on

[1] Unless otherwise indicated, all materials are held and distributed by the National Institute for Biological Standards and Control, Potters Bar, Herts, EN6 3QG, the United Kingdom.

regulatory considerations for the evaluation of mRNA vaccines, which could be updated as more scientific and clinical data became available. A draft document had been developed with sections covering general considerations, quality issues, and preclinical and clinical assessment. It was proposed that an appendix be added to address issues specific to SARS-CoV-2 mRNA vaccines.

3. Following a review of the range of vaccine platforms currently being used to develop SARS-CoV-2 candidate vaccines, and of the challenges of ensuring their safety and efficacy, the ECBS identified a need for both written and measurement standards to support such vaccine development. In particular, guidance was needed on the design, validation and standardized comparison of antibody assays. Guidance was also needed on the measurement and standardization of cellular immune responses, specifically with regard to safety issues. Furthermore, there are currently no guidelines specifically for SARS-CoV vaccines or more generally for vaccines based on RNA platforms. In addition, despite no evidence to date that SARS-CoV-2 candidate vaccines cause vaccine-associated enhanced respiratory disease, an analogous effect has been reported in a SARS-CoV-1 mouse model and rigorous assessment of this would be required.

4. Proposals for the development of two international standards for use in public health emergencies were also endorsed at the current meeting: the First WHO International Standard for SARS-CoV-2 RNA for NAT-based assays and the First WHO International Standard for anti-SARS-CoV-2 antibodies. The first is urgently needed to standardize diagnostic assays, which are essential both for clinical treatment and for containing outbreaks. The second is essential for: (a) the standardization of assays used to measure antibody responses elicited by vaccination; (b) diagnosing previous exposure to SARS-CoV-2; and (c) standardizing SARS-CoV-2 antibody content in COVID-19 convalescent plasma (CCP). Related issues include a lack of knowledge regarding the quality of the various antigen targets used for ELISA and the need for standard antigen preparations to facilitate the standardization of antibody binding assays.

5. The COVID-19 pandemic has adversely impacted upon the supply of blood and blood components in many countries. The ECBS was updated on the latest WHO guidance on maintaining a safe and adequate blood supply during the pandemic, and on the safe collection of CCP. Evidence indicates that the treatment of patients with CCP is a potentially effective therapy. It is essential that virus neutralizing antibody levels are standardized to facilitate consistent treatment. It was the strongly held view of the ECBS that CCP should be calibrated in IU as soon as the antibody standard became available.

6. High-throughput deep sequencing technology is proving to be increasingly important as an alternative to supplement or replace the currently recommended adventitious virus detection assays performed on biological medicines. Two proposals were presented to the ECBS on the development of reference standards for adventitious virus detection in biological products using next-generation sequencing. These proposals provide an example of how the rapid evolution of highly sophisticated assay technologies is increasingly impacting upon the work of the ECBS.

The next meeting of the ECBS is scheduled for 19–23 October 2020.