Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 20 to 24 March 2023

The 77th meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held virtually from 20 to 24 March 2023. In addition to its ongoing work in relation to the COVID-19 pandemic, the ECBS also provided advice on a range of other biological standardization issues. ECBS members, regulatory authority representatives and subject matter experts from governmental organizations participated in the meeting from Monday 20 March to Thursday 23 March 2023. A short open information-sharing session involving all participants, including non-state actors, was held on Monday 20 March 2023. 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 24 March 2023 attended only by ECBS members and WHO staff. At the end of the closed session, the ECBS provided its feedback and recommendations to WHO on a number of current issues in biological standardization. A full meeting report will be published in the WHO Technical Report Series in 2023.

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

- **Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases**

  Monoclonal antibody (mAb) products currently represent the largest class of therapeutic proteins in clinical use. Technological advances in mAb engineering have led to the development of a wide range of such products and at its meeting in April 2022 the ECBS had recommended the adoption of the WHO Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use. However, an increasing number of mAbs are now being developed specifically for the prevention or treatment of infectious diseases. In addition, the COVID-19 pandemic has highlighted the potential benefits of such products when rapidly responding to public health emergencies caused by emerging infectious agents. Recognizing the paucity of regulatory advice specific to the evaluation of mAbs and related products for use against infectious pathogens and their toxins, the ECBS recommended the adoption of the above WHO Guidelines. The document provides regulatory guidance in this key area and is intended to facilitate harmonization of relevant global regulatory requirements, accelerate approval processes and increase access to such products, while continuing to assure their safety and efficacy.

- **Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products**

  Rapid advances in the use of human cells, tissues and gene therapies to treat serious diseases have resulted in a wide range of products that differ considerably in their degree of complexity. These products can broadly be divided into the two categories of human cells and tissues (HCTs) and advanced therapy medicinal products (ATMPs). These hugely diverse product categories pose significant regulatory challenges that could undermine their global accessibility, and appropriate and safe use. While many countries have little or no regulatory framework for HCTs and/or ATMPs, others have established their own national regulatory frameworks and guidance. Following a recent WHO-led

review, the ECBS had previously advised that global regulatory convergence in this area was now of paramount importance. The above high-level considerations document represents the first step in addressing this issue. The document sets out the fundamental principles, concepts and key features of effective regulatory oversight of HCTs and ATMPs, defines key terms, proposes a template for product-categorization decisions and provides an annotated bibliography of useful references and resources.

As shown in Table 1, the ECBS recommended the establishment of eight new and three replacement WHO international reference materials. The ECBS also endorsed 12 proposals to establish future international reference materials. In addition, the ECBS recommended that two further antibody preparations be added to the First WHO International Reference Panel of antibodies to SARS-CoV-2 variants of concern established at its previous meeting, and endorsed a pilot study to explore the potential utility of a prospective reference reagent for lipid-nanoparticle-encapsulated messenger RNA (mRNA) products.

Table 1
WHO international reference materials established by the ECBS in March 2023

Material	Unitage	Status
Biotherapeutics (other than blood products)		
Human VEGF165	9000 IU/ampoule	First WHO International Standard
Blood products and related substances		
Blood coagulation factor VIII concentrate	9.5 IU/ampoule	Ninth WHO International Standard
In vitro diagnostics		
Human leukocyte antigen antibodies (negative plasma)	No unitage assigned	WHO International Reference Reagent
Human leukocyte antigen antibodies (negative serum)	No unitage assigned	WHO International Reference Reagent
Human leukocyte antigen antibodies (strong positive plasma)	No unitage assigned	WHO International Reference Reagent
Human leukocyte antigen antibodies (weak positive plasma)	No unitage assigned	WHO International Reference Reagent
Anti-citrullinated protein/peptide antibodies	260 IU/ampoule	First WHO International Standard
Hepatitis B virus DNA for NAT-based assays	5.69 $\log_{10}$ IU/vial	Fifth WHO International Standard

Vaccines and related substances		
Meningococcal serogroup C polysaccharide	0.965 ± 0.024 mg/ampoule	Second WHO International Standard
Rift Valley fever virus antibodies for use in neutralization assays (human plasma)	250 IU/ampoule	First WHO International Standard
Rift Valley fever virus antibodies for use in binding assays (human plasma)	250 IU/ampoule (anti-glycoprotein immunoglobulin G)	First WHO International Standard

In addition to recommending the adoption of the two WHO documents and the establishment of the 11 reference materials described above, the ECBS also discussed the following issues:

1. Reflecting on standardization issues relating to the COVID-19 pandemic – and specifically on the way in which the pandemic had driven the rapid development of novel prophylactic and therapeutic products – the ECBS applauded the efforts of WHO in delivering highly relevant documents and reference materials under considerable time pressures. The ECBS noted that since 2020 five such WHO documents had been drafted, subjected to public consultations and adopted, including the above WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases. With the support of partner organizations – in particular the Coalition for Epidemic Preparedness Innovations (CEPI) and the Medicines and Healthcare products Regulatory Agency National Institute for Biological Standards and Control (MHRA–NIBSC) – WHO had also established a comprehensive package of reference materials that were now being used to underpin the development of urgently needed vaccines, biotherapeutics and diagnostics. Faced with an evolving antigenically diverse pathogen such as SARS-CoV-2, maintaining stocks of relevant reference materials presents particular challenges. Relevant decisions taken at the current meeting included the above two recommendations by ECBS to expand the First WHO International Reference Panel for antibodies to SARS-CoV-2 variants of concern to include antibodies to Gamma and Omicron variants, and to conduct a pilot study on the potential utility and primary users of a WHO reference reagent for lipid-nanoparticle-encapsulated mRNA products.

2. The Committee was provided with an update of efforts to evaluate the potential benefits of convalescent plasma as a treatment for SARS-CoV-2 infection, mainly as a high-titre product early in the disease course. Although this approach has been used previously to treat other infectious diseases, there is conflicting evidence regarding its efficacy in this context. Data analysis, including systematic reviews, has not demonstrated clear efficacy for such use in moderate to severe SARS-CoV-2 infections but there is some evidence that it may benefit a subset of immunocompromised individuals. However, the optimal dose and frequency of administration remain uncertain, with the quantification of “high-titre” products also requiring further consideration. In addition, the collection of plasma from recovered individuals may impose significant burdens on blood centres without clear evidence of efficacy. The systematic review data had been discussed during a meeting of

the WHO Advisory Group for Blood Regulation, Availability and Safety, and further review in collaboration with the International Society of Blood Transfusion will be conducted.

3. The ECBS discussed the long-recognized challenge of assigning units to WHO antibody reference materials used to harmonize different types of antibody assays. This issue had once again been highlighted following establishment of the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin. Although there was good evidence that this standard had been helpful in harmonizing both antibody neutralization assays and antibody binding assays, the use of different unit names to distinguish between these two functions had led to criticism from users and from metrology specialists that such an approach was potentially confusing. Prior to the current ECBS meeting, an ad hoc working group had been convened to review the issues and to propose an approach that could be applied to antibody standards with potential utility in both neutralization and binding assays. After reviewing the options put forward by the working group, consensus was reached among ECBS members that such reference standards should be split into two separate materials. For each material, the standard name itself should clearly indicate the category of assay for which it was intended, with the respective instructions for use reinforcing this distinction. The ECBS then discussed in more detail the conventions to be followed when naming such reference materials, including ensuring the more consistent use of qualifiers where required. Accepting that already established standards could only switch to the standardized nomenclature at replacement, the ECBS supported the implementation of the agreed convention to new or replacement standards with immediate effect where possible.

4. During discussion of the laboratory studies conducted to establish the above WHO reference materials, a recurring theme was the apparently limited number and geographical representativeness of study participants. A number of recent challenges in this regard were brought to the attention of the ECBS, including the increased workload of potential participants during the COVID-19 pandemic, increasingly demanding shipping requirements affecting the distribution of collaborative study materials, and the use of technologically more sophisticated and costly assays. Noting that the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards recommended, but did not require, that collaborative studies involve laboratories in all six WHO regions, the ECBS advised that in all cases the study design should be based on a clear scientific rationale and should ensure sufficient statistical power to support its conclusions. In this respect, consideration must be given to any potential variations that may impact upon the use of an assay and its associated reference material, including for example variations in regional disease incidence and genetic differences both across different populations and in locally circulating pathogen strains. The Committee also highlighted the potentially beneficial involvement of WHO regional offices on a case-by-case basis in the identification of collaborative study participants.

The next meeting of the ECBS is scheduled for 16–20 October 2023.