

Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 4 to 8 April 2022

The 75th meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held virtually from 4 to 8 April 2022 as part of implementing a biannual meeting schedule intended to expedite the establishment of WHO measurement standards. In addition to its ongoing work in relation to the COVID-19 pandemic, the ECBS covered 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 4 April to Thursday 7 April 2022. A short open information-sharing session involving all participants, including non-state actors, was held on Monday 4 April 2022. 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 8 April 2022 attended only by ECBS members and WHO staff. The ECBS also provided advice and recommendations to WHO on a number of key issues in biological standardization. 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 three WHO written standards:

- **Guidelines on evaluation of biosimilars**

The WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) were adopted in 2009 and have served as the basis for national regulatory frameworks for the licensure of such products. However, in light of the subsequent World Health Assembly resolution WHA67.21 on access to biotherapeutics, along with technological advances in the production and characterization of biotherapeutic products, the ECBS at its meeting in October 2020 had recommended reviewing current scientific evidence and experience to inform revision of the 2009 WHO Guidelines. The scope of the revised Guidelines was expanded to include the evaluation of biological products other than biotherapeutics, with a corresponding shift to the use of the term “biosimilar” rather than “similar biotherapeutic product”. To allow for greater flexibility and reduced regulatory burden, while at the same time continuing to ensure the quality, safety and efficacy of such products, the sections on quality, and nonclinical and clinical evaluation were revised in line with current practices and other guidance. The revised Guidelines are intended to provide globally acceptable principles for the licensing of biosimilars of originator products licensed on the basis of a full licensing dossier. It is expected that this will help to harmonize global regulatory requirements and accelerate the approval of, and access to, such products while continuing to assure their quality, safety and efficacy.

- **Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use**

Therapeutic monoclonal antibody (mAb) products have become increasingly important over the last 25 years and are now the predominant treatment for a wide variety of diseases. Although the majority of approved therapeutic mAbs have been developed for the treatment of noncommunicable diseases, their short development time, good safety characteristics and rapid effect also make them highly suitable for use during public health emergencies such as the COVID-19 pandemic. However, it has become clear that limited experience in the regulation of mAb-based products in low- and middle-income countries,

and a lack of regulatory harmonization globally, are among the factors currently restricting the wider availability of such products. On the advice of the ECBS, two updated WHO Guidelines were developed to help address these and other issues. The above document, recommended by the ECBS for adoption at the current meeting, covers the production and quality control of mAbs intended for medicinal use. The Guidelines apply to mAbs and related products such as conjugates, fragments and mAb cocktails, and provide guidance relevant to most production systems, including plant-based production systems. The second document on the preclinical and clinical evaluation of mAbs for use in the prevention and treatment of infectious diseases will be reviewed by the ECBS at a future meeting.

- **WHO manual for the preparation of reference materials for use as secondary standards in antibody testing**

A core function of WHO is to establish and promote International Standards for food, biological, pharmaceutical and similar products. While WHO International Standards serve as primary measurement standards and are considered to be of the “highest order”, secondary standards are normally prepared by national control laboratories and manufacturers as working standards to avoid rapid depletion of the often limited supply of the corresponding International Standard. In addition to the WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards, WHO has also published manuals on the development of secondary standards specifically used for the evaluation of vaccines and in vitro diagnostics. Following feedback received by WHO, a need was identified for a corresponding WHO manual on the preparation, calibration and use of secondary standards used in antibody testing. Such a need was reinforced by the unprecedented level of demand for the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin. The above manual provides guidance on the preparation, characterization, calibration, storage and distribution of antibody secondary standards, and was recommended by the ECBS for adoption.

As shown in Table 1, the ECBS recommended the establishment of five new WHO international reference materials. The ECBS also endorsed three proposals for future international reference materials.

Table 1. WHO international reference materials established by the ECBS in April 2022

Material	Unitage	Status
In vitro diagnostics		
Anti-human neutrophil antigen-3a immunoglobulin G	1 in 8 dilution assigned as the minimum potency	WHO International Reference Reagent
Lassa virus RNA for NAT-based assays	4.0 log ₁₀ IU/ampoule	First WHO International Standard
Anti-β2GPI immunoglobulin G	200 IU/vial	First WHO International Standard
Standards for use in high-throughput sequencing technologies		

Reference reagents for microbiome analysis	No unitage assigned	WHO international reference reagents
Vaccines and related substances		
Anti-EV-D68 serum (human)	1000 IU/ampoule	First WHO International Standard

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

1. Standardization issues relating to the ongoing COVID-19 pandemic continue to form a major part the ECBS agenda and both the WHO Guidelines for the production and quality control of mAbs and the WHO manual on secondary standards used in antibody testing outlined above will have direct relevance to the development and assessment of COVID-19 therapeutics and vaccines. In addition, the ECBS was informed that unprecedented global demand for the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin established in December 2020 had resulted in its depletion by August 2021, with more than 2400 units shipped to 581 individual users. This level of demand was attributed to the unavoidable lack of secondary standards early in the pandemic and misuse of the reference material for assay validation rather than calibration. Candidate replacement materials are currently being evaluated and it is anticipated that a replacement standard will be presented to the ECBS for consideration in October 2022. In addition, a panel of sera containing antibodies against SARS-CoV-2 variants of concern is being evaluated in neutralization and antibody binding assays. This panel will support the ongoing development of serological assays, and allow for assessment of their ability to detect such variants. With regard to preparedness for future pandemics, discussion took place on the lessons learnt from the COVID-19 pandemic, including the need to improve the way in which candidate reference materials are sourced, for example through the establishment of a WHO Biohub and other repository initiatives. There is also a need for educational tools on calibration methods to ensure the appropriate use of WHO reference materials. An update was also provided on the status of a prospective SARS-CoV-2 antigen standard scheduled for presentation to the ECBS in October 2022. Such a standard would provide a much-needed common reference material for the comparative evaluation, post-marketing surveillance and quality assurance of antigen-based SARS-CoV-2 diagnostic tests.
2. In 2019, the ECBS endorsed a 3-year project to review the animal testing requirements and methods described in WHO Guidelines on the quality control and lot release of vaccines and biotherapeutic products. The purpose of the review was to: (a) determine the type and extent of animal testing recommended; (b) identify any currently available 3R (Replace, Refine, Reduce) strategies not currently considered; (c) identify and explore potential barriers to the adoption of 3Rs principles by regulators and manufacturers; and (d) identify WHO strategies to support the adoption of the 3Rs principles. To avoid any perception of bias arising from WHO reviewing its own documents, the review was being conducted by the independent National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) in the United Kingdom. The ECBS was informed of progress made during the first phase of the project, including the production of an interim report and associated recommendations of an international working group of experts tasked with reviewing the WHO documents. These recommendations include using language that emphasizes the scientific benefits of adhering to the 3Rs principles and ensuring consistency of language across different guidelines when recommending animal-based and alternative

quality control and lot release methods. Five focus groups had now been established to evaluate the potential for adoption of 3Rs principles in tests for potency/immunogenicity, pyrogenicity/endotoxin, neurovirulence, adventitious agents and specific toxicity, and draft text in these areas will be proposed for use in future WHO guidelines. In addition, surveys among manufacturers and regulators had been conducted to elicit their views on the implementation of 3Rs approaches. Recognizing the significant influence of WHO in driving changes in the use of animals for product testing, the Committee applauded the progress made by this project. Once the final report on the first phase of the project is presented to ECBS in 2023, consideration would be given to recommending the drafting of a WHO position paper and guidance on the incorporation of 3Rs principles and practices into lot release testing, and to the development of specific WHO guidance on endotoxin and pyrogen testing.

3. ECBS reviewed the current WHO priorities for the development of new and revised WHO written standards for biological products. Regarding COVID-19-related documents, the ECBS noted that in addition to the two relevant documents recommended for adoption at the current meeting, WHO guidance on plasmid DNA vaccines and mRNA vaccines had been adopted in 2020 and 2021 respectively. It was also anticipated that WHO Guidelines on the preclinical and clinical evaluation of mAbs used for the prophylaxis and treatment of infectious diseases would be presented for consideration in April 2023. Subject to further consideration, this document may incorporate a number of disease-specific supplements, for example on COVID-19 and respiratory syncytial virus, with further supplements on rabies, malaria and human immunodeficiency virus potentially added subsequently. In addition, it was recommended that several existing and possibly outdated WHO written standards (for example, on oral poliomyelitis vaccines, and yellow fever, rotavirus, malaria, dengue and MMR vaccines) should be revised in order to reflect new manufacturing technologies and quality control methods, and to improve consistency with other WHO written standards. Furthermore, depending on the outcome of ongoing vaccine developments in the respective fields, new WHO guidelines may be required (for example, on vaccines against tuberculosis, Shigella and group B streptococcus). A number of more general WHO documents may also require revision or amendment, including WHO guidelines on pandemic influenza preparedness, lot release, post-approval changes and the evaluation of mAbs for use as biosimilars. The adoption of the related WHO Guidelines on evaluation of biosimilars outlined above will be complemented by the development of biosimilar product-specific case studies. In light of this package of revised WHO guidance on biosimilars, the ECBS advised that the 2018 WHO Questions and Answers: similar biotherapeutic products document should now be withdrawn from the WHO website. Finally, the WHO Recommendations for the preparation, characterization and establishment of international and other reference standards will be reviewed during 2022–2023 with a view to developing two separate documents to provide guidance to custodian laboratories and to the end users of such standards.

The next meeting of the ECBS is scheduled for 24-28 October 2022.