## **Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 11 to 14 March 2024**

The 79th meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held virtually from 11 to 14 March 2024. ECBS members, regulatory authority representatives and subject matter experts from governmental organizations participated in the meeting from Monday 11 to Wednesday 13 March 2024. A short open information-sharing session involving all participants, including non-state actors, was held on Monday 11 March 2024. 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 Thursday 14 March 2024 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. The full meeting report will be published in the WHO Technical Report Series later this year.

A wide range of biological standardization issues were discussed, including issues arising from the ongoing coronavirus disease 2019 (COVID-19) outbreak. The main meeting outcomes included the recommended adoption of the following WHO document:

**Nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of COVID-19**

* Cases of COVID-19 continue to occur worldwide, with the causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreading widely and causing severe disease and in some cases long COVID, including among highly vulnerable groups. It is anticipated that as COVID-19 becomes endemic, it will continue to cause severe illness, hospitalizations and deaths as new variants emerge. In March 2023, the WHO Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases were adopted on the advice of the ECBS. This document provides guidance on the evaluation of monoclonal antibodies (mAbs) and related products regardless of the target pathogen or toxin. During the adoption of these Guidelines, the ECBS recognized the need to also develop a number of addenda on disease-specific regulatory considerations. Following demonstration during the COVID‑19 pandemic of the importance of mAbs in responding to public health emergencies caused by emerging infectious agents, the ECBS recommended the adoption of the above first such addendum, which sets out a number of specific issues to be considered when evaluating the safety and efficacy of mAb products directed against SARS-CoV-2. The ECBS also highlighted the potential utility of the principles set out both in the parent Guidelines and the above addendum in the broader context of responding to epidemics and pandemics caused by other rapidly evolving respiratory disease pathogens.

As shown in Table 1, the ECBS also recommended the establishment of five new WHO international reference materials. In addition, it endorsed seven proposals to establish future new and replacement materials.

Table 1

**WHO international reference materials established by the ECBS in March 2024**

|  |  |  |
| --- | --- | --- |
| **Material** | **Unitage** | **Status** |
| **Biotherapeutics other than blood products** | | |
| Golimumab | 500 IU/ampoule TNF neutralizing activity  500 IU/ampoule of TNF binding activity  500 IU/ampoule of FcγRIII binding activity  500 IU/ampoule of ADCC activity  50 μg/ampoule for therapeutic drug monitoring | First WHO International Standard |
| **In vitro diagnostics** | | |
| HIV-1 p24 antigen | 44 IU/ampoule | First WHO International Standard |
| Lassa virus RNA for NAT-based assays  Lineages II, III, V and VII | No unitage assigned | First WHO International Reference Panel |
| **Standards for use in high-throughput sequencing technologies** | | |
| Adventitious virus detection in biological products using HTS technologies | CBER-FSCUST-90 (hCoV)  2.6 x 1010 genome copies/mL  CBER-FSCUST-91 (PCV1)  8.1 x 109 genome copies/mL  CBER-FSCUST-92 (REO)  1.5 x 1010 genome copies/mL  CBER-FSCUST-93 (FeLV)  4.0 x 1010 genome copies/mL  CBER-FSCUST-94 (EBV)  2.8 x 107 genome copies/mL  CBER-FSCUST-95 (RSV)  5.5 x 1010 genome copies/mL  CBER-FSCUST-96 (MVM)  1.2 x 1010 genome copies/mL | First WHO International Reference Panel |
| **Vaccines and related substances** | | |
| Diphtheria antitoxin for use in flocculation test (equine) | No unitage assigned | WHO International Reference Reagent |

As shown in Table 2, the ECBS also considered the proposed discontinuation of seven existing WHO international reference materials.

Table 2

**WHO international reference materials proposed for discontinuation in March 2024**

|  |  |  |
| --- | --- | --- |
| **Material** | **Rationale** | **Proposed discontinuation pathway** |
| First WHO International Standard for calcitonin, ASU 1–7 eel calcitonin analogue (elcatonin)  **NIBSC code 84/614** | Low, and highly geographically restricted, demand | Decision by the ECBS in October 2024 based on the outcomes of stakeholder consultation and feedback |
| First WHO International Standard for human C-reactive protein  **NIBSC code 85/506** | Low demand as a result of limited adoption of the assigned IU | Decision by the ECBS in October 2024 based on the outcomes of stakeholder consultation and feedback |
| WHO international reference reagents for adventitious virus detection by high-throughput sequencing  Porcine circovirus type 1  **CBER code SC-VR-6000P**  Mammalian orthoreovirus type 1  **CBER code SC-VR-6001P**  Feline leukaemia virus  **CBER code: SC-VR-6002P**  Human respiratory syncytial virus  **CBER code: SC-VR-6003P**  Epstein-Barr virus  **CBER code: SC-VR-6004P** | Superseded by the establishment of the First WHO International Reference Panel (see Table 1 above) | Recommendation by the ECBS to establish the reference panel at the current meeting resulted in immediate discontinuation of all five WHO international reference reagents and their reassignment as CBER reagents for research purposes only |

The Committee also agreed that a decision would be made at its next meeting in October 2024 on a proposal not to proceed with a previously endorsed project to develop an antibody standard for A(H7N9) influenza virus. Changes in zoonotic influenza epidemiology since 2018 meant that pandemic preparedness efforts were now focused on other influenza subtypes and it has not been possible to source the serum-positive samples needed to prepare the candidate material.

In addition to the above specific recommendations and proposals in relation to WHO written and measurement standards, the ECBS also discussed the following broader issues:

1. Despite the recommendation of the ECBS in 2018 not to include any mention of the innocuity test (also known as the general safety test or abnormal toxicity test) in future WHO Recommendations, Guidelines and other guidance documents on the evaluation of biological products, such testing continues to be widely conducted despite the absence of any scientific rationale for its use. This has, in part, been attributed to the use of older WHO Guidelines and Recommendations that are yet to be revised. The ECBS welcomed a proposal to specifically highlight this issue and to list all affected documents in future ECBS reports published in the WHO Technical Report Series. It was envisaged that as such documents were suitably revised, their number would decrease until the list was no longer required. The Committee suggested that similar guidance on the removal of the innocuity test also be provided on the WHO website, including on the webpages providing links to the relevant WHO documents.
2. The ECBS noted that several WHO international reference materials established recently would be directly relevant in furthering efforts to implement the 3Rs principles (Replacement, Reduction, Refinement) for minimizing the use of animals in biological product quality control and lot-release testing. Among these, the First WHO International Reference Panel for adventitious virus detection in biological products using high-throughput sequencing technologies established at the current meeting would support the wider use of such highly advanced and sensitive non-animal methods, with considerable benefits envisaged in accelerating testing timelines and thus expediting access to safe and affordable biological products.
3. One of the strategic objectives of the WHO Action Framework to advance universal access to safe, effective and quality-assured blood products 2020–2023 is the establishment of functioning and efficiently managed blood services. However, a lack of knowledge in implementing and maintaining good manufacturing practices (GMP) in blood establishments has been identified as a common barrier to ensuring functional and good quality systems. Recognizing the importance of, and pressing need for, WHO guidance to countries in this area, the ECBS expressed its support for a proposal by the WHO Advisory Group on Blood Regulation, Availability and Safety to revise the 2011 WHO Guidelines on GMP for blood establishments. It was intended that the revised document would reflect new developments in this field and provide countries with practical guidance on how to establish reliable quality assurance systems for the whole chain of blood collection, testing, processing and distribution of blood components in blood establishments and hospital blood banks.
4. The ECBS felt that specific mention of relevant WHO international reference standards in respective Recommendations, Guidelines and other WHO written standards should continue as this helps to increase awareness of the availability and importance of such standards. However, in documents such as the addendum on the evaluation of mAbs against COVID-19 adopted at the current meeting, it was noted that there was a possibility that some of the standards listed may be replaced relatively quickly or more directly suitable standards established following document publication. Therefore, the ECBS advised that a short text be added in all documents that listed such standards to inform users of the importance of consulting the WHO Biologicals website to ensure the appropriate use of the most up-to-date reference materials.

**The next meeting of the ECBS is scheduled for 7–11 October 2024**