

Report on meetings of expert committees and study groups¹

Report by the Director-General

BIOLOGICAL STANDARDIZATION

Seventy-seventh report of the Expert Committee on Biological Standardization, virtual meeting,² 20–24 March 2023³

1. The Expert Committee on Biological Standardization reviews developments in the field of biological products used in human medicine. Such products include vaccines, biotherapeutics, blood products, cell, tissue and gene therapy products, and in vitro diagnostics. The Committee coordinates activities leading to the adoption of WHO recommendations, guidelines and guidance documents (written standards) that help to ensure the quality, safety and efficacy of such products, as well as to the establishment of WHO international reference standards (measurement standards) required for the global harmonization of associated laboratory data.
2. The adoption and publication of WHO written standards and the establishment and use of WHO measurement standards designating the activity of biological products used for the diagnosis, prevention or treatment of disease allow for the comparison of nonclinical and clinical data worldwide. Ensuring the comparable quality, safety and efficacy of biological products is a vital step in facilitating their equitable global availability and thus contributes towards attainment of the key strategic WHO goal of universal health coverage.
3. During its seventy-seventh meeting, the Committee made recommendations on a broad range of recent WHO activities, including several biological standardization activities relating to the continuing coronavirus disease (COVID-19) pandemic.

¹ The Regulations for Expert Advisory Panels and Committees provide that the Director-General shall submit to the Executive Board a report on meetings of expert committees containing observations on the implications of the expert committee reports and recommendations on the follow-up action to be taken.

² Coordinated from WHO headquarters, Geneva.

³ WHO Technical Report Series, No. 1048, 2023.

Main recommendations

4. Following detailed discussion and review, the Committee recommended the adoption of two WHO written standards:

- (a) Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases; and
- (b) Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products.

5. Following careful consideration of the reports of international collaborative laboratory studies, the Committee also recommended the establishment of 11 new or replacement WHO measurement standards. In addition, the Committee endorsed 12 proposals to develop new or replacement WHO measurement standards.

6. The Committee discussed and made recommendations on a number of priority standardization issues in relation to the COVID-19 pandemic. Noting the considerable challenges of developing appropriate biological written and measurement standards in a timely manner during public health emergencies, the Committee applauded the continuing efforts of WHO. The Committee went on to recommend that the previously established First WHO International Reference Panel for antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern be expanded to include antibodies to Gamma and Omicron variants. In addition, the Committee expressed its support for a pilot study on the potential utility and primary users of a WHO reference reagent for lipid-nanoparticle-encapsulated messenger RNA products.

7. The Committee reviewed the long-standing practice of establishing WHO antibody standards in International Units explicitly for use in neutralization assays while allowing the same material to be used to compare antibody binding assays using the arbitrary Binding Antibody Unit. Although widely accepted in the field, this pragmatic approach has led to criticism from sections of the metrology community. Noting the potential for confusion and associated risk of loss of confidence in WHO international standards, the Committee had previously requested that an ad hoc working group be convened to review the issues and to identify options regarding the best way forward. This working group had subsequently met and following presentation of its proposals, a strong consensus was reached by the Committee that such reference standards should henceforth 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.

8. During discussion of the results of a number of laboratory studies to establish WHO measurement standards, the Committee noted the apparently small number and limited geographical representativeness of study participants. A number of recent challenges in this regard were highlighted, including the increased workload of potential participants during the COVID-19 pandemic, increasingly demanding shipping requirements for collaborative study materials, and the use of technologically more sophisticated and costly assays. Noting that WHO's own published guidance recommended, but did not require, that collaborative studies involve laboratories in all six WHO regions, the Committee advised that each collaborative study be considered on a case-by-case basis. Nevertheless, in all cases, the study design should be based on a clear scientific rationale and should ensure sufficient statistical power to support its conclusions. Consideration must also be given to any potential geographical variations that may have an impact on the use of an assay and its associated reference material, such as variations in regional disease incidence, and/or genetic differences both across different populations and between

locally circulating pathogen strains. The Committee also highlighted the potentially beneficial involvement of WHO regional offices in the identification and recruitment of suitable study participants.

9. The Committee reviewed current WHO priorities for the development of new and revised WHO written standards for biological products. The Committee indicated its overall support for the approach taken, and for the specific proposals made in relation to the development or revision of product-specific and more general WHO recommendations, guidelines and guidance documents.

Significance for public health policies

10. As with all WHO written standards, the two that were recommended for adoption at the seventy-seventh meeting of the Committee are scientific and advisory in nature and are intended to provide accurate, up-to-date guidance to national regulatory authorities and to manufacturers of biological products. If so desired, such guidance, suitably modified where required, may be adopted as definitive national regulatory requirements by countries.

11. Monoclonal antibody products currently represent the largest class of therapeutic proteins in clinical use. Technological advances in their engineering have now led to the development of a wide range of such products. The above-mentioned Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases will help to harmonize relevant global regulatory requirements, accelerate approval processes and increase access to these key products, while continuing to assure their safety and efficacy.

12. 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 hugely diverse and complex products pose significant regulatory challenges that could undermine their global accessibility, and appropriate and safe use. The above-mentioned Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products represents a welcome first step in the regulatory harmonization of such products, which often address otherwise unmet medical needs. The document sets out the fundamental principles, concepts and key features of effective regulatory oversight in this area, defines key terms and proposes a template for product-categorization decisions.

13. The timely availability of internationally recognized WHO measurement standards remains crucial for countries and manufacturers in harnessing the benefits of scientific advances in the production and evaluation of vital biological products. The establishment of the 11 new or replacement WHO measurement standards recommended by the Committee will directly facilitate the broader and more equitable availability of such products and thus contribute towards attainment of the global public health goal of universal health coverage.

Implications for the Organization's programmes

14. The Committee's review and approval of proposed WHO priorities for the development of new and revised WHO written standards for biological products is an important step in ensuring that published WHO guidance on the development, manufacture and regulation of biological products remains relevant and up to date.

15. The development, establishment and promotion of globally required biological measurement standards remain core normative WHO activities as set out in its Constitution. The decision of the Committee to recommend establishment of the 11 new or replacement WHO measurement standards

will directly support the continuation of these core activities. In addition, the endorsement by the Committee of the proposed future development of 12 new or replacement WHO measurement standards will ensure that priority standards continue to become available in a timely manner to support the work of WHO programmes in addressing both the existing and emerging global health priorities of the Organization.

16. The decisions and recommendations of the Committee have direct implications for the regulation and quality control of biological products and are thus relevant not only to regulators in all countries but also to the numerous programmes and initiatives within WHO and other international organizations that rely upon the availability of vaccines, biotherapeutics, blood products, cell, tissue and gene therapy products, in vitro diagnostics and other biological products.

SELECTION AND USE OF ESSENTIAL MEDICINES

Report of the twenty-fourth meeting of the Expert Committee on the Selection and Use of Essential Medicines, Geneva, 24–28 April 2023¹

Main recommendations

17. The Expert Committee on the Selection and Use of Essential Medicines reviewed 85 applications proposing amendments to the WHO Model List of Essential Medicines and/or the WHO Model List of Essential Medicines for Children (the Model Lists). The Committee recommended the addition of 24 new medicines to the WHO Model List of Essential Medicines and 12 new medicines to the WHO Model List of Essential Medicines for Children. Six medicines were recommended for deletion. A total of 32 applications proposing amendments to one or both of the Model Lists, involving 41 medicines, were not recommended. Medicines on the 2023 WHO Model List of Essential Medicines and WHO Model List of Essential Medicines for Children number 502 and 361, respectively.

18. Three new medicines for the treatment of multiple sclerosis were recommended to be added to the WHO Model List of Essential Medicines (cladribine, glatiramer acetate and rituximab) based on evidence of benefits and safety. Rituximab is used off-label for this disease. Ocrelizumab, an on-label medicine in the same class as rituximab, was not recommended for inclusion as there was no evidence of greater benefit than rituximab and higher price.

19. Other recommended new additions to the Model Lists include three single-pill combinations of medicines to prevent atherosclerotic cardiovascular diseases, two medicines for cancer, five medicines for infectious diseases, a medicine for epilepsy and four medicines for mental health and substance use.

20. Medicines not recommended for addition to the Model Lists include medicines for the treatment of dementia due to Alzheimer disease, weight loss in obesity, and for the treatment of spinal muscular atrophy, sunscreen for the prevention of skin cancer in people with albinism or xeroderma pigmentosum, and 10 medicines for treatment of cancer.

¹ WHO Technical Report Series, No. 1049 (in press).

Significance for public health policies

21. The Model Lists provide evidence-informed guidance to Member States for developing or updating national essential medicines lists. The Model Lists represent a prioritization tool for the selection, procurement, reimbursement and use of essential medicines at country level, as part of efforts to ensure access to medicines and universal health coverage.

22. Medicine labelling is the responsibility of national regulatory authorities, and there may consequently be different labels for the same product in different countries. There is thus no global standard for what is considered “off-label”. WHO recommendations for listing medicines for off-label uses as essential reflect that there is sufficient evidence to demonstrate effectiveness and safety, and in many cases, financial advantages in comparison with on-label alternatives, and signals to countries that off-label essential medicines may be considered for national selection and use, where permitted. It is a responsibility of national decision-makers to consider national labelling and legal requirements in the selection and use of off-label medicines at country level.

23. Decisions not to recommend some medicines for listing despite evidence of effectiveness, safety and public health relevance were often because of prohibitively high prices and unsustainable budget impact. Such high prices and budget impact continue to signal the need for global and national strategies and interventions aimed at reducing prices to facilitate affordability and access.

Implications for the Organization’s programmes

24. The update of the Model Lists informs and supports the work of WHO disease programme areas and contributes to delivery of consistent recommendations across the Organization through alignment between the Model Lists and WHO guidelines and other WHO guidance documents.

25. With the recommended addition to the WHO Model List of Essential Medicines of single-pill combinations of medicines to prevent atherosclerotic cardiovascular diseases, the Committee recommended that WHO evaluate the potential benefits of developing guidance specific for clinical use and national implementation of these combinations, to supplement existing guidance.

26. The Committee recommended that WHO revise the procedures for updating the Model Lists. Since the procedures were last revised in 2001,¹ evaluation of medicines has become increasingly complex, and the 2001 procedures are no longer considered fully fit-for-purpose.

27. The work of the Committee has been facilitated by expert working groups on antimicrobials and cancer medicines. Sustained activities of the working groups will continue to support the Committee and the broader work of corresponding WHO programme areas.

¹ See document EB109/8.

EVALUATION OF CERTAIN FOOD ADDITIVES

Ninety-sixth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, 27 June–6 July 2023¹

Main recommendations

28. The report contains the Joint FAO/WHO Expert Committee on Food Additives' evaluations of technical, toxicological and epidemiological data, including the occurrence of and dietary exposure to the food additive aspartame.
29. The Committee also assessed dietary exposure to two groups of flavouring agents (esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids and hydroxy- and alkoxy-substituted benzyl derivatives) and revised the specifications for eight flavouring agents.
30. Specifications for the following food additives were revised: lycopene (synthetic), lycopene from *Blakeslea trispora*, pentasodium triphosphate and steviol glycosides.
31. The assessments, recommendations and comments by the Committee will be discussed by the Codex Committee on Food Additives in order to generate recommendations to national authorities to identify and recommend appropriate risk-management and risk-mitigation measures to reduce human exposure, where necessary.
32. WHO will publish detailed monographs in the WHO Food Additives Series with the toxicological and other related information upon which the safety assessments of the compounds were based.² FAO publishes summaries of the identity and purity of previous cargoes and contaminants.

Significance for public health policies

33. The Committee identifies and, where possible, quantifies the public health significance of exposure to chemicals in food – in these cases, food additives including flavouring agents – through scientific risk assessment based on international consensus. When a health concern is identified, clear recommendations are issued for action by national governments or through the relevant organs of the Joint FAO/WHO Food Standards Programme.
34. The Committee's recommendations are used by the Codex Alimentarius Commission in the development of international food safety standards and other guidance and recommendations. Such standards are science based and are established only for substances that have been evaluated by the Committee. This ensures that food commodities that are traded internationally meet strict safety standards to protect the health of the consumer and ensure fair practices in food trade.
35. The advice provided by the Committee is also considered by Member States directly when national or regional food safety standards are being established.

¹ WHO Technical Report Series, No. 1050 (in press).

² Safety evaluation of certain food additives. WHO Food Additives Series, No. 87. Toxicological monographs of the ninety-sixth meeting (in preparation).

36. The Committee's work, in its complexity and in reaching an international scientific consensus on the evaluation of these compounds, is unique in its importance for and impact on global public health decisions related to food safety.

Implications for the Organization's programmes

37. The evaluation of chemicals in food by the Committee is a continuing activity. Five meetings of the Committee on food additives were held in the biennium 2022–2023.¹ Three of the meetings focused on evaluating the safety of food additives, one on contaminants in food and one on residues of veterinary drugs in food.

38. WHO is a partner in the Joint FAO/WHO Food Standards Programme, whose principal organ is the Codex Alimentarius Commission. In its capacity to assure the sound scientific basis for international standards and recommendations on food additives, contaminants in food and veterinary drug residues in food, the work of the Committee is crucial to the work of the Codex Alimentarius Commission.

39. The Committee's evaluations are also used by Heads of WHO offices in countries, territories and areas and by regional offices when advice is provided to Member States on food safety issues.

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¹ For more information, see [https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-\(jecfa\)](https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)) (accessed 12 July 2023).