

Report on meetings of expert committees and study groups¹

Report by the Secretariat

BIOLOGICAL STANDARDIZATION

Sixty-seventh report of the Expert Committee on Biological Standardization, Geneva, 17–21 October 2016²

1. The Expert Committee on Biological Standardization reviews developments in the field of biological substances used in human medicine, which include vaccines, biological therapeutics, blood products and related in vitro diagnostic devices. It coordinates activities leading to the adoption of recommendations for assuring the quality, safety and efficacy of such substances and the establishment of international reference materials.

Main recommendations

2. The use of international reference materials for designating the activity of biological substances used in prophylaxis or therapy, or for ensuring the reliability of quality control or diagnostic procedures, allows comparability of data worldwide. On the basis of the results of international collaborative laboratory studies, the Expert Committee established 14 new or replacement WHO international biological reference preparations.³ These are the primary calibrants against which regional or national measurement standards are benchmarked.⁴ The following guidance, as contained in the Annexes to the Expert Committee's sixty-seventh report, was also adopted:

- Annex 2: Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products

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 WHO Technical Report Series, No. 1004, 2017.

³ WHO Technical Report Series, No. 1004, Annex 11, 2017.

⁴ An up-to-date list of WHO international biological reference preparations is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 11 May 2017).

- Annex 3: Guidelines on management of blood and blood components as essential medicines
- Annex 4: Guidelines on estimation of residual risk of HIV, hepatitis B virus or hepatitis C virus infections via cellular blood components and plasma
- Annex 5: Guidelines for the production, control and regulation of snake antivenom immunoglobulins
- Annex 6: WHO manual for the preparation of secondary reference materials for in vitro diagnostic assays designed for infectious disease nucleic acid or antigen detection
- Annex 7: Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine producing countries
- Annex 8: Labelling information of inactivated influenza vaccines for use in pregnant women
- Annex 9: Guidelines on clinical evaluation of vaccines: regulatory expectations
- Annex 10: Human challenge trials of vaccine development: regulatory considerations.

3. The Expert Committee endorsed plans for WHO to initiate new work on the standardization of cell therapy products and agreed that the development of reference preparations for gene therapy products should be explored further.

4. The Expert Committee also provided advice to WHO on the written standards and reference preparations under development and on the plans for submission to the Expert Committee in 2017–2019.

Significance for public health policies

5. The standardization of biologicals has risen to be high on the agenda of Member States.¹ The work of the Expert Committee is directly relevant to this agenda.

6. A need for specific guidance for the evaluation of monoclonal antibodies as similar biotherapeutic products was identified through a WHO consultation in 2015. The guidelines adopted by the Expert Committee² respond to this need and to resolution WHA67.21 (2014). Monoclonal antibodies are a major class of biotherapeutic products that has achieved outstanding success in treating many life-threatening and chronic diseases. Some of these therapeutic products are ranked in the top 10 lists of annual global pharmaceutical revenue successes. As patents and data protection measures on monoclonal antibodies products have expired, or are nearing expiry, considerable attention has turned towards producing biotherapeutic products similar to the approved monoclonal antibodies innovator products, with a view to making these products more affordable and to improve global access. The new guidelines will facilitate regulatory evaluation of this class of products.

¹ See resolution WHA67.21 (2014) on access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy.

² WHO Technical Report Series, No. 1004, Annex 2, 2017.

7. The Expert Committee established the first WHO International Standard for Zika virus RNA for nucleic acid amplification technology-based assays.¹ This reagent was developed and evaluated in a very short period of time in order to respond to the Zika virus disease outbreak, which constituted a public health emergency of international concern. The reagents provide stakeholders with internationally validated calibrants with which diagnostic tests and assay results from clinical trials can be expressed in a common unitage.

Implications for the Organization's programmes

8. Guidance on regulatory approaches for marketing authorization of pandemic influenza vaccines² and on arrangements for lot release of these vaccines during a public health emergency was developed in the context of the Pandemic Influenza Preparedness Framework's Partnership Contribution Implementation Plan for regulatory capacity-building and strengthening of pandemic preparedness and response. The guidelines developed target, in particular, non-vaccine-producing countries. Furthermore, the Strategic Advisory Group of Experts on immunization recommends the immunization of pregnant women with trivalent inactivated influenza vaccine at any stage of pregnancy. However, for various reasons, the implementation of influenza immunization during pregnancy remains suboptimal. One reason is the perceived risk of administering influenza vaccine, or indeed any vaccine, to this population group especially in view of the precautionary language used in some product labels. Guidelines adopted by the Expert Committee provides a clear statement, which indicates that, on the basis of current evidence, the use of inactivated influenza vaccine in pregnant women is not contraindicated.³ It is expected to facilitate maternal immunization programmes by raising awareness of the convergence of regulatory positions in spite of differing approaches to labelling and regulatory language regarding the use of these vaccines in pregnant women worldwide.

9. Snake bites have a significant global impact on health: an estimated 5 million people are bitten by snakes every year, leading to around 100 000 deaths and leaving 400 000 people permanently disabled or disfigured. Antivenoms are so far the only effective therapy. WHO introduced the first round of antivenom assessment in 2016 in an effort to enhance antivenom production. The WHO guidelines for the production, control and regulation of snake antivenom immunoglobulins were revised⁴ in response to developments in the field. These included changes in technologies, the identification of new snake species, and taxonomic name changes. Improving the quality and safety of antivenoms is crucial to restoring confidence in antivenom immunotherapy, particularly in resource-poor nations. It is anticipated that application of the principles in these guidelines will address this issue and lead to increased use of antivenoms and improved outcomes.

10. The WHO prequalification of in vitro diagnostics aims at promoting and facilitating access to safe, appropriate and affordable in vitro diagnostics of good quality in an equitable manner. For the prequalification of in vitro diagnostics, WHO reference materials are needed to support verification and validation studies, performance evaluations, as well as post-market surveillance of in vitro diagnostics in countries. However, the use of the WHO International Standards is limited so that the stocks do not need to be replaced on a regular basis. The calibration of a secondary reference material

¹ WHO Technical Report Series, No. 1004, section 7.1.1, 2017.

² WHO Technical Report Series, No. 1004, Annex 7, 2017.

³ WHO Technical Report Series, No. 1004, Annex 8, 2017.

⁴ WHO Technical Report Series, No. 1004, Annex 5, 2017.

against the WHO standard is thus required, but this is a complex process. New guidance was therefore established on how to produce and evaluate secondary reference materials for in vitro diagnostics.¹

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Fifty-first report of the Expert Committee on Specifications for Pharmaceutical Preparations, Geneva, 17–21 October 2016²

11. The Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General in the area of medicines' quality assurance. It provides independent expert recommendations and guidance to ensure that medicines meet standards of quality worldwide. Its advice is developed through a broad consensus-building process and covers all areas of quality assurance of medicines, from their development to their distribution to patients.

Main recommendations

12. In the area of quality control, the Expert Committee endorsed WHO's continued support of the Member States' pharmacopoeias and the international meetings of world pharmacopoeias. The meetings are organized by WHO; in 2016, the meeting was co-hosted by the Japanese Pharmacopoeia Commission. The Expert Committee recommended the continuation of the External Quality Assurance Assessment Scheme for quality control laboratories; it adopted 17 new specifications and general texts for inclusion in *The International Pharmacopoeia* and four International Chemical Reference Substances established by the European Directorate for the Quality of Medicines and Health Care, which is the custodian centre for International Chemical Reference Substances. Moreover, the Committee endorsed the revised concepts and future perspectives of *The International Pharmacopoeia*³ aimed at enhancing synergies, saving resources and improving the service to meet public health needs.

13. In the areas related to quality assurance, the Expert Committee adopted the WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines.⁴ The Expert Committee further agreed to revise the procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies, for the prequalification of quality control laboratories.⁵

14. The WHO guidelines on multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability⁶ were supplemented by specific advice on equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System.⁷ The list of international

¹ WHO Technical Report Series, No. 1004, Annex 6, 2017.

² WHO Technical Report Series, No. 1003, 2017.

³ WHO Technical Report Series, No. 1003, Annex 2, 2017.

⁴ WHO Technical Report Series, No. 1003, Annex 1, 2017.

⁵ WHO Technical Report Series, No. 1004, Annex 3, 2017.

⁶ WHO Technical Report Series No. 992, Annex 7, 2015.

⁷ WHO Technical Report Series, No. 1003, Annex 6, 2017.

comparator pharmaceutical products needed to assess the interchangeability of multisource products was revised and adopted together with its general background notes.¹

15. Furthermore, the Expert Committee adopted the new WHO global model regulatory framework for medical devices including in vitro diagnostic medical devices.² This new regulatory framework is intended to be used by national regulatory agencies in order to formulate laws and regulations to define and control the national market in medical devices in the interest of public health. This was in response to resolution WHA67.20 (2014) on regulatory system strengthening for medical products, including medical devices, which urges Member States to strengthen national regulatory systems.

Significance for public health policies

16. The Expert Committee provides a wide spectrum of written and physical standards to test medicines for their quality, together with a range of guidelines, good practices and regulatory guidance in the area of medicines' quality assurance. These are designed to serve all Member States, especially their national and regional regulatory authorities, organizations of the United Nations system and regional and interregional harmonization efforts. They underpin important public health initiatives, including the prequalification and procurement of quality medicines through major international bodies, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations, such as UNICEF.

17. The Expert Committee responds to the increasing demands and international need in the area of medicines' quality assurance and related regulatory aspects, covering the entire life cycle of medicines, from their development to distribution to the patient.

18. Much of the Expert Committee's work is aimed at increasing the convergence in the area of quality assurance and regulatory guidance, to facilitate efficient synergies among and within the respective authorities and pharmacopoeias, and to reduce duplication of efforts and thus costs. The outcome is intended to protect patients and facilitate access to quality medicines.

Implications for the Organization's programmes

19. The Expert Committee responds to the needs of major public health interests as identified by other WHO programmes. The outcomes and recommendations of this Expert Committee have broad implications for inter- and intra-cluster relationships, for links with regional offices, country offices and partnerships, as well as for the work of other WHO expert committees. This Expert Committee's work enables WHO to fulfil its constitutional mandate in the area of medicines' quality assurance and is of relevance for all within WHO who are involved with medicines.

20. The Expert Committee especially serves WHO's Prequalification Team and its Regulatory Systems Strengthening Team. Both teams benefit from the availability of the international guidelines, standards and specifications recommended by the Expert Committee. In return, they provide practical feedback to the Expert Committee through their direct links to those who implement the more than 80 current guidelines and 700 specifications.

¹ WHO Technical Report Series, No. 1003, Annex 5, 2017.

² WHO Technical Report Series, No. 1003, Annex 4, 2017.

21. Through the Expert Committee's recommendations, WHO is in a position to offer technical scientific advice to all those dealing with the development, production, quality control, regulatory pathways, inspection, supply and procurement of medicines. WHO offers tools for implementation by its own programmes, Member States and non-State actors, which can help to ensure that quality medicines reach the patients, and which can contribute to universal health coverage.

22. The following guidelines and guidance, as contained in the Annexes to the Expert Committee's fifty-first report, were adopted and recommended for use:

- Annex 1: WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines (new)
- Annex 2: The International Pharmacopoeia: revised concepts and future perspectives (update)
- Annex 3: Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (update)
- Annex 4: WHO global model regulatory framework for medical devices including in vitro diagnostic medical devices (new)
- Annex 5: General background notes on the list of international comparator pharmaceutical products (new) together with the updated list of international comparator products for equivalence assessment of interchangeable (generic) products
- Annex 6: Guidance on equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System, as Appendix 2 to the WHO guidelines on multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (new).

DRUG DEPENDENCE

Thirty-eighth report of the Expert Committee on Drug Dependence, Geneva, 14–18 November 2016¹

23. A total of 12 new psychoactive substances were assessed by the Expert Committee on Drug Dependence and recommendations for placing 10 new psychoactive substances under international control were conveyed to the Commission on Narcotic Drugs, which made the final decision on scheduling in March 2017. The Expert Committee recommendation was based on evidence of substantial public health risks.

¹ WHO Technical Report Series, No. 1005, 2017.

Main recommendations

24. The Expert Committee recommended that the substances listed below should be placed under international control:

(a) in Schedule I of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol:

- U-47700, chemical name: 3,4-dichloro-*N*-(2-dimethylamino-cyclohexyl)-*N*-methylbenzamide
- Butyrfentanyl (butyrylfentanyl), chemical name: *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]butanamide

(b) in Schedule II of the Convention on Psychotropic Substances of 1971:

- 4-methylethcathinone (4-MEC), chemical name: 2-(ethylamino)-1-(4-methylphenyl)propan-1-one
- Ethylone (3,4-methylenedioxy-*N*-ethylcathinone; bk-MDEA; MEDEC), chemical name: 1-(2H-1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one
- Pentedrone (α -methylaminovalerophenone), chemical name: 2-(methylamino)-1-phenylpentan-1-one
- Ethylphenidate (EPH), chemical name: ethyl phenyl(piperidin-2-yl)acetate
- Methiopropamine (MPA), chemical name: *N*-methyl-1-(thiophen-2-yl)propan-2-amine
- MDMB-CHMICA, chemical name: methyl *N*-{[1-(cyclohexylmethyl)-1H-indol-3-yl]carbonyl}-3-methyl-L-valinate
- 5F-APINACA (5F-AKB-48), chemical name: *N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide
- XLR-11, chemical name: 1-(5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone

25. The Expert Committee recommended that the following substances should not be placed under international control:

- JWH-073, chemical name: (1-butyl-1H-indol-3-yl)(1-naphthyl)methanone

Owing to the current insufficiency of data regarding dependence, abuse and risks to public health, the Expert Committee recommended not to place JWH-073 under international control, but to continue to keep it under surveillance.

26. The Expert Committee recommended that a critical review¹ should be carried out for a subsequent Expert Committee meeting:

- 3-Methylmethcathinone (3-methyl-N-methylcathinone; 3-MMC), chemical name: 2-(methylamino)-1-(3-methylphenyl)propan-1-one

The Expert Committee decided that the information available was inadequate to enable a consensus and a confident recommendation regarding the scheduling of 3-MMC. The Expert Committee requested the Secretariat to arrange another critical review of 3-MMC for a subsequent meeting of the Expert Committee.

27. The Expert Committee recommended pre-reviews² on cannabis. At its thirty-seventh meeting, in November 2015, the Expert Committee requested the Secretariat to begin collecting data towards a pre-review of cannabis, cannabis resin, extracts and tinctures of cannabis at a future meeting. Two updates on the scientific literature on cannabis were prepared and presented to the thirty-eighth meeting of the Expert Committee.

The Expert Committee at its thirty-eighth meeting recognized:

- an increase in the use of cannabis and its components for medical purposes;
- the emergence of new cannabis-related pharmaceutical preparations for therapeutic use;
- that cannabis has never been subject to a formal pre-review or critical review by the Expert Committee.

The Expert Committee requested the Secretariat to prepare relevant documentation in order to conduct pre-reviews for the following substances:

- cannabis plant and cannabis resin
- extracts and tinctures of cannabis
- delta-9-tetrahydrocannabinol (THC)
- cannabidiol (CBD)
- stereoisomers of delta-9-tetrahydrocannabinol.

The Expert Committee recommended that a specific meeting of the Expert Committee, dedicated to cannabis and its component substances, should be held within 18 months of the thirty-eighth meeting.

¹ Critical review: a review to make decisions on scheduling or a change in scheduling.

² Pre-review: an initial review to determine whether a critical review is warranted.

Other matters

28. As requested by the Expert Committee at its thirty-seventh meeting, a meeting of an informal working group in May 2016 revised the templates of the critical review reports and the WHO questionnaire for psychoactive substances. These new templates were used for the critical reviews and for collecting country information that was presented at the thirty-eighth meeting of the Expert Committee.

29. A second meeting of the informal working group will meet in May 2017 to prioritize substances for review by the Expert Committee at its thirty-ninth meeting and to develop a strategy for the five recommended pre-reviews of cannabis.

Significance for public health policies

30. The substances that were recommended for scheduling by the Expert Committee at its thirty-eighth meeting were considered to present risks in terms of abuse and public health harm. On 16 March 2017, during the sixtieth session of the Commission on Narcotic Drugs, the Commission decided to include all 10 substances in the relevant conventions.

31. Consistent with the Commission resolution 59/8 (2016) on promotion of measures to target new psychoactive substances and amphetamine-type stimulants, the Secretariat is developing a surveillance system, complementary to the scheduling process, in response to the need for rapid communication of the dangers associated with new psychoactive substances. The system will accumulate data continuously through collaborative arrangements with multiple organizations (for example, UNODC and the European Monitoring Centre for Drugs and Drug Addiction) and Member States, and will support the prioritization process of substances to be considered by the Expert Committee. The list of substances under surveillance is available on the WHO website.¹

Implications for the Organization's programmes

32. The Secretariat advocates and supports the implementation of policies that aim for a balance between improving the availability of controlled medicines and preventing their misuse, diversion and trafficking, in line with the international drug control conventions. The Joint Global Programme on access to controlled drugs for medical purposes, while preventing diversion and abuse is the result of cooperation between WHO, the Union for International Cancer Control and UNODC, to improve access to controlled medicines, particularly pain medication. The Secretariat has provided support to the Democratic Republic of the Congo and Timor-Leste and has planned activities for tackling barriers to access to controlled medicines for pain in these countries. At regional meetings held in Egypt, Kenya and Thailand, the Secretariat delivered presentations on WHO's role under the international drug control conventions and promoted the use of the WHO guidelines and other documents on access to controlled medicines

ACTION BY THE EXECUTIVE BOARD

33. The Board is invited to note the report.

¹ See <http://www.who.int/medicines/access/controlled-substances/substancesundersurveillance.pdf?ua=1> (accessed 17 May 2017).