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Reports on meetings of expert committees and study groups¹

Report by the Director-General

BIOLOGICAL STANDARDIZATION

Sixty-ninth report of the Expert Committee on Biological Standardization Geneva, 29 October–2 November 2018²

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

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.³

Main recommendations

3. Based on the results of international collaborative laboratory studies, the Expert Committee established 15 new or replacement WHO international biological reference preparations.⁴ These are the primary standards intended for use as calibrants against which secondary standards (for example, regional or national measurement standards) are benchmarked.

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. 1016, 2019.

³ An up-to-date list of all WHO's international biological reference preparations is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 11 March 2019).

⁴ WHO Technical Report Series, No. 1016, 2019, Annex 5; for the main outcomes of the meeting and new and replacement standards, see https://www.who.int/biologicals/expert_committee/ECBS_Executive_Summary_final_20_NOV_2018.IK.pdf?ua=1 (accessed 18 March 2019).

4. In addition, the Expert Committee recommended the adoption of three written standards and complementary material to the existing standard on similar biotherapeutic products:

- recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines¹
- guidelines for the safe development and production of vaccines to human pandemic influenza viruses and influenza viruses with pandemic potential²
- guidelines for the safe production and quality control of poliomyelitis vaccines³

WHO Questions and Answers: similar biotherapeutic products

5. The Expert Committee also provided advice to the Director-General on the written standards and reference preparations under development and on the plans for submission to the Expert Committee in 2019–2020.

6. The Expert Committee recognized that the standardization of cellular and gene therapies should be included in the work of WHO as an area of great importance from the global public health perspective. The Expert Committee noted the recommendation of the International Conference of Drug Regulatory Authorities that WHO develop, in collaboration with Member States, a “state-of-the-art” document capturing areas where agreement among experienced regulatory authorities exists. The Expert Committee encouraged the assignment of appropriate resources to the setting up of a working group on the standardization of cellular and gene therapies to take this work forward.

Significance for public health policies

7. WHO’s new recommendations on recombinant hepatitis E vaccines for regulators, manufacturers and vaccine developers provide guidance on their manufacturing and nonclinical and clinical evaluation. The adoption of this document will enable the licensing, subsequent prequalification and use of hepatitis E vaccines in outbreak areas to prevent hepatitis E virus infection.

8. The recommended guidelines for the safe development and production of vaccines to human pandemic influenza viruses and influenza viruses with pandemic potential replace the previous guidelines adopted by the Expert Committee in 2005. The revision takes into account the considerable experience gained from handling both highly pathogenic avian viruses and those classified as low virulence for avian species but highly virulent for humans. The revised guidelines also specify the measures to be taken to prevent or minimize the risk to workers involved in the development and production of such vaccines, and the risk of virus release into the environment, including the risk of transmission to animals.

9. WHO’s guidelines for the safe production and quality control of poliomyelitis vaccines, also adopted by the Expert Committee, are of strategic importance for the Global Polio Eradication Initiative and its endgame strategic plan. The revised guidelines address the containment measures needed during the production and quality control of inactivated polio vaccine produced both from wild poliovirus strains and from the live attenuated vaccine (Sabin) strains used in the manufacture of oral polio vaccine.

¹ WHO Technical Report Series, No. 1016, Annex 2, 2019.

² WHO Technical Report Series, No. 1016, Annex 3, 2019.

³ WHO Technical Report Series, No. 1016, Annex 4, 2019.

The document replaces WHO's guidelines issued in 2004 for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses. The Expert Committee recommended that consideration be given to holding implementation workshops to ensure that regulators, poliomyelitis vaccine manufacturers, researchers and public health officials were aware of and understood the updated guidelines. It was emphasized that the document should be read in conjunction with the global action plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use (GAPIII) and with the reports of the Containment Advisory Group.

10. The standardization of biological therapeutic medicines has been recognized by Member States as a priority in order to increase access to these products. The work of the Expert Committee related to biotherapeutics, including similar biotherapeutic products, is contributing to the implementation of resolution WHA67.21 (2014) on access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy. In that context, the document with the WHO questions and answers on similar biotherapeutic products was prepared to complement WHO's guidelines on evaluation of similar biotherapeutic products adopted by the Committee in 2009. Those guidelines have been used as a basis for establishing national regulatory requirements for the evaluation of such products for the purpose of licensing. The Expert Committee recognized that the guidelines from 2009 remained valid and did not therefore require revision at this point. The Expert Committee approved the resulting document with questions and answers and recommended that it be posted on the WHO website attached to the 2009 guidelines rather than published as an annex to the report of the Expert Committee.

Implications for the Organization's programmes

11. The Expert Committee recommended that henceforth, with immediate effect, all WHO's future documents on vaccines and other biologicals published in the Technical Report Series (including WHO's recommendations, guidelines and manuals) should not include a recommendation for conducting the innocuity test. It was agreed that a statement should be made in the full report of the Expert Committee indicating that the inclusion of this test in previously published WHO Technical Report Series documents should now be disregarded. This represents a significant step towards science-based regulation and regulatory convergence at the global level.

12. The Expert Committee emphasized that the standardization of priority pathogens for public health emergencies should remain a priority for WHO. As an example, the First WHO International Standard for Anti-Asian lineage Zika virus antibody (human), established by the Expert Committee in 2018, could be used in diagnosis, vaccine evaluation and serosurveillance. The establishment of this reference material is a major step forward in supporting preparedness for public health emergencies.

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Fifty-third Expert Committee on Specifications for Pharmaceutical Preparations Geneva, 22–26 October 2018¹

13. The Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General in the area of medicines' quality assurance. Its advice is developed through a broad consensus-building process based on wide public consultation, following an established process, and it

¹ WHO Technical Report Series, No. 1019, 2019
(https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1019/en/).

covers all areas of quality assurance of medicines throughout their life cycle and across supply chains from development to distribution to patients.

Main recommendations

14. The Expert Committee adopted nine guidelines and 12 pharmacopoeial texts (two general chapters and 10 new and revised monographs) for inclusion in *The International Pharmacopoeia* and confirmed the release of 10 new International Chemical Reference Substances established by the WHO custodian centre.

15. The following guidelines and decisions were adopted and recommended:

- procedure for development of the WHO medicines quality assurance guidelines;
- guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems – illustrative part;
- revised guidance on good manufacturing practices for validation, including the general main text, analytical procedure validation, validation of computerized systems and qualification;
- in the area of interchangeability of multisource medicines, a set of priorities was agreed for the development of a proposal to waive *in vivo* bioequivalence requirements for medicines included in the WHO Model Lists of Essential Medicines. The outcome of a pilot study was confirmed and the Protocol to conduct equilibrium solubility experiments for the purpose of biopharmaceutics classification system-based classification of active pharmaceutical ingredients for biowaiver was adopted;
- *Guidelines on import procedures for pharmaceutical products*;
- *Good practice guidance document on implementing the collaborative procedures*.

16. Furthermore, the Expert Committee recommended the continued offering of the External Quality Assurance Assessment Scheme for national quality control laboratories and the update of the process for the WHO certification scheme on the quality of pharmaceutical products moving in international commerce and its procedure with the active involvement of Member States.

Significance for public health policies

17. The increasing globalization of commerce and trade and internationalization of pharmaceutical production result in medicines that are often designed for use outside the country of manufacture. The Expert Committee provides a wide spectrum of international written and physical standards to ensure that medicines are of quality during their full life cycle from development to distribution to patients across the increasingly complex supply chain, often spanning across continents. Much of its work aims to increase 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. These standards are designed to serve all Member States, especially their national and regional regulatory authorities, organizations in the United Nations system and regional and inter-regional harmonization efforts, and to underpin important public health initiatives, including the prequalification and procurement of high-quality medicines through intergovernmental

organizations, such as UNICEF, and major international bodies, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria.

18. The goal of the Expert Committee's work is to contribute effectively and efficiently to the achievement of the Sustainable Development Goals and universal health coverage targets, to support the broadening and extension of access to high-quality, safe, effective and affordable medicines.

Implications for the Organization's programmes

19. The Expert Committee's work provides international norms and standards for quality assurance of medicines developed through a wide global consultation process with relevance throughout the Secretariat for all whose work concerns medicines. The outcome and recommendations of the Expert Committee have broad implications across the Organization's programmes and offices, including regional and country offices as well as for its partnerships and the work of other Expert Committees. This Expert Committee especially serves WHO's Prequalification of Medicines and Regulatory Systems Strengthening teams through the availability of WHO's international guidelines, standards and specifications. In return, practical feedback is provided to the Expert Committee through the direct link to those who implement the more-than-90 current guidelines and 700 specifications. The Expert Committee provides international norms and standards to determine the quality of medicines globally, assists WHO to fulfil its normative role and contributes effectively to the Director-General's strategy for reaching the triple billion goals.

DRUG DEPENDENCE

Forty-first report of the Expert Committee on Drug Dependence Geneva, 12–16 November 2018¹

20. WHO is mandated by the International Drug Control Conventions to evaluate the scientific evidence related to dependence, abuse and harm to health of psychoactive substances and their therapeutic use. This is done through the Expert Committee on Drug Dependence which issues recommendations on whether psychoactive substances should be placed under international control.

Main recommendations

21. The Expert Committee reviewed 16 psychoactive substances and made the following recommendations:

New psychoactive substances. The Expert Committee recommended placing nine new psychoactive substances under international control. These include four fentanyl analogues that have contributed to opioid overdose deaths around the world, four synthetic cannabinoids and one cathinone (a stimulant).

Medicines. The Committee recommended that tramadol should not be internationally controlled at this time because of the lack of alternative analgesics for the treatment of moderate-to-severe pain in many low-income countries and in crisis situations. in addition, the Expert Committee

¹ WHO Technical Report Series, No. 1018, 2019.

recommended not to schedule pregabalin at this time. Both substances should remain under surveillance so that the harms that they present to public health can be monitored.

Cannabis and cannabis-related substances. The Expert Committee recognized the public health harms presented by these substances, as well as their potential for therapeutic and scientific use. As a result, it recommended a more rational level of control for cannabis and cannabis-related substances that would prevent drug-related harms while ensuring that cannabis-derived pharmaceutical preparations are available for medical use.

22. These recommendations have been communicated to the Secretary-General of the United Nations and will be subject to a vote by the Member States of the United Nations Commission on Narcotic Drugs in Vienna.

Significance for public health policies

23. The Expert Committee's recommendations ensure that psychoactive substances are available for medical and scientific purposes, while preventing them from being diverted and causing harm to health. The Expert Committee's recommendations to place psychoactive substances under international control mean that countries should enforce certain restrictions on the import, export, possession and use of controlled substances.

24. New psychoactive substances such as fentanyl analogues have no therapeutic use and have contributed to substantial numbers of deaths by overdose. The Expert Committee recommended that these substances be placed under international control to restrict their use and prevent the harm they can cause.

25. Medicines such as tramadol are crucial for the treatment of pain in low-income countries and emergency situations where controlled opioids such as morphine may not be available. The Expert Committee acknowledged the increase in the number of reports of tramadol abuse and dependence in some countries, including some on the use of falsified and substandard tramadol. The Expert Committee's recommendations aimed to ensure that tramadol is available for legitimate medical use, while preventing harm caused by its misuse.

26. The Expert Committee recognized recent developments in the medical use of cannabis and cannabis components. Many countries are embarking on the development and implementation of policies that permit the use of cannabis-related products for medical purposes. The recommendations facilitate the appropriate medical use of cannabis-related products with proven efficacy and enable further research on those uses, while protecting against their misuse through applying appropriate levels of international control for cannabis and its components. It is expected that the recommendations will contribute to better availability of cannabis-based pharmaceutical preparations because of greater clarity in the implementation of the international conventions in countries.

Implications for the Organization's programmes

27. To ensure that medicines such as opioids are available for legitimate use where they are needed, for example in the treatment of pain, the secretariat of the Expert Committee works closely with the Expert Committee on the Selection and Use of Essential Medicines which is responsible for revising and updating the WHO Model List of Essential Medicines. This collaboration aims to ensure that robust evidence-based information is shared on the appropriate use of controlled medicines for various conditions, including the management of pain and palliative care. The secretariat of the Expert

Committee also works closely with WHO's programmes on HIV/AIDS and mental health towards addressing in an integrated manner the public health dimension of the global drug problem.

28. The recommendations of the Expert Committee carry important implications for countries, and WHO's regional and country offices have a paramount role in raising awareness of the public health risks of psychoactive substances, supporting countries in the monitoring of drug-related harm through ongoing data collection, and promoting the use of guidelines for the appropriate use of medicines and the prevention and treatment of drug disorders at country level.

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