

Report on meetings of expert committees and study groups¹

Report by the Director-General

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Fifty-fourth Expert Committee on Specifications for Pharmaceutical Preparations Geneva, 14–18 October 2019²

1. The Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General in the area of medicines' quality assurance and provides regulatory tools for medical products. Its advice is developed through a broad consensus-building process based on wide public consultation, following an established process, and covers all areas of quality assurance of medicines throughout their life cycle and across supply chains from development to distribution to patients.

Main recommendations

2. The Expert Committee adopted 13 guidelines and 16 pharmacopoeial texts for inclusion in The International Pharmacopoeia and confirmed the release of six International Chemical Reference Substances established by the custodian centre.

3. The following guidelines and decisions were adopted:

- Procedure for the development of monographs and other texts for inclusion in The International Pharmacopoeia
- International Atomic Energy Agency and WHO guidelines on good manufacturing practices for radiopharmaceuticals
- Production of water for injection by means other than distillation
- Good chromatography practices

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. 1025, 2020.

- Quality management system requirements for national inspectorates
- Points to consider for manufacturers and inspectors: environmental aspects of manufacturing practices for the prevention of antimicrobial resistance
- Good storage and distribution practices
- Points to consider for setting the remaining shelf-life of medical products upon delivery
- WHO/United Nations Population Fund prequalification programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices
- WHO/United Nations Population Fund technical specification for male latex condoms
- WHO/United Nations Population Fund specifications for plain lubricants
- WHO “Biowaiver List”: proposal to waive in vivo bioequivalence requirements for medicines of immediate-release, solid oral dosage forms included in the WHO Model List of Essential Medicines
- WHO guideline on the implementation of quality management systems for national regulatory authorities.

4. Furthermore, it was recommended to continue the External Quality Assurance Assessment Scheme to build the capacity of quality-control laboratories and to continue updating the WHO certification scheme on the quality of pharmaceutical products moving in international commerce with the active participation of Member States.

Significance for public health policies

5. Much of the Expert Committee’s work is aimed at increasing the convergence in the area of quality assurance and regulatory guidance in order to facilitate synergies among and within the respective authorities and pharmacopoeias, and to reduce the duplication of efforts and, thus, costs.

6. The Expert Committee’s technical guidance on medicines quality is designed to serve regulatory authorities of all Member States, as well as organizations in the United Nations system and other major international bodies. The Committee also provides a technical platform for convergence as recommended by the International Conference of Drug Regulatory Authorities.

7. At a time when access to essential medicines is a pressing issue on the sustainable development agenda, the Expert Committee’s standard-setting work makes a unique and critical contribution towards more equitable access to needed medicines of assured quality. The Committee also recommends regulatory guidelines of importance to multisource medicines designed to be used globally, be it in hot and humid climates, small or big countries, or well- or less-developed settings. The outcome is intended to protect patients and facilitate access to high-quality medicines as a response to the new global agenda, articulated in the 2030 Agenda for Sustainable Development, prioritizing inter alia universal health coverage. This Committee actively contributes to bringing about access to quality essential medicines and health products for all.

Implications for the Organization's programmes

8. The outcomes and recommendations of this Expert Committee have broad inter- and intra-cluster relationships, links with regional offices, country offices and partnerships, as well as connections with other Expert Committees, whenever the subject of medicines arises. The international, globally-applicable norms and standards help to ensure that high-quality medicines reach patients.

9. The Expert Committee especially serves the WHO Prequalification Unit – Medicines and Regulatory Systems Strengthening teams, as well as the disease programmes. In return, practical feedback is provided directly to the Expert Committee by those who implement the comprehensive set of more than 100 current guidelines, 590 specifications and 250 International Chemical Reference Substances. The Expert Committee's work provides international norms and standards – developed through a wide global consultation process – for medicines' quality assurance and regulatory tools, with relevance for all involved with medicines within WHO.

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Eighty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, 22–31 October 2019¹

Main recommendations

10. The report contains the Expert Committee's evaluations of technical, toxicological, epidemiological, occurrence and dietary exposure data for seven veterinary drug residues: two antimicrobial agents (fosfomycin and halquinol), an acaricide (ethion), two antiparasitic agents (ivermectin and selamectin), and two insecticides (diflubenzuron and flumethrin). In addition, the Expert Committee had issued a call for data to evaluate sisapronil (an ectoparasiticide); however, as no additional data were submitted, the evaluation could not proceed for this veterinary drug.

11. The report also presents general considerations and guidance, in particular for updated methodological approaches for assessment of veterinary drug residues in food.

12. The assessments, recommendations and comments provided by the Expert Committee will be discussed by the Codex Committee on Residues of Veterinary Drugs in Food and will result in the identification of appropriate risk management and risk-mitigation measures to reduce human exposure where necessary, and in recommendations to national authorities for the safe use of these veterinary drugs in food-producing animals.

13. WHO will publish detailed monographs in the WHO Food Additives Series of the toxicological, epidemiological and other related information upon which the health risk assessments of the compounds were based.

Significance for public health policies

14. The Expert Committee identifies and, if possible, quantifies the public health significance of exposure to residues of veterinary drugs in food through scientific risk assessment based on international consensus. When a health concern is identified, clear recommendations are issued for action by national

¹ WHO Technical Report Series, No. 1023, 2020.

governments or through the Joint FAO/WHO Food Standards Programme (the Codex Alimentarius Commission and its subsidiary bodies).

15. The Expert 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 Expert 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.

16. The advice provided by the Expert Committee is also considered by Member States directly when national or regional food safety standards are being established.

17. All Member States face the problem of assessing the potential health risks of chemicals in food; however, only a few scientific national and regional institutions systematically assess all relevant toxicological, epidemiological and related data. It is therefore important that the reports of the Expert Committee provide Member States with valid information on both the general aspects of risk assessment and the specific evaluations of the veterinary drugs mentioned above.

18. The Expert 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

19. The evaluation of chemicals in food by the Expert Committee is an ongoing activity. Four meetings of the Expert Committee were held in the biennium 2018–2019.¹

20. 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 veterinary drug residues in food, the work of the Expert Committee is crucial to the work of the Codex Alimentarius Commission.

21. The Expert 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.

BIOLOGICAL STANDARDIZATION

Seventieth report of the Expert Committee on Biological Standardization Geneva, 21–25 October 2019²

22. The Expert Committee on Biological Standardization reviews developments in the field of biological substances used in human medicine, which include vaccines, biotherapeutics, blood products and related substances and in vitro diagnostic reagents. It coordinates activities leading to (a) the

¹ For publications see <https://www.who.int/foodsafety/publications/jecfa-reports/en/> (accessed 23 March 2020).

² WHO Technical Report Series, No. 1024, 2020.

adoption of guidelines and recommendations for assuring the quality, safety and efficacy of such substances and (b) the establishment of international standards and other reference materials.¹

23. 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.

Main recommendations

24. Based on the results of international collaborative laboratory studies, the Expert Committee established 32 new or replacement WHO international biological reference preparations. These are the primary standards intended for use as calibrants against which secondary standards (for example, regional or national measurement standards) are benchmarked.

25. The Committee also recommended the adoption of two written standards:

- Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines;
- Amendment to Annex 3 of WHO Technical Report Series, No. 993, Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated).

26. The Committee also provided advice to the Director-General on the written standards and reference preparations under development as well as on the proposals scheduled for submission to the Committee in 2020–2021.

27. The 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 Committee noted the recommendation of the International Conference of Drug Regulatory Authorities that the Secretariat develop, in collaboration with Member States, a state-of-the-art document capturing areas where agreement among experienced regulatory authorities exists. The Committee encouraged the Secretariat to assign 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

28. WHO's new Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines (2019) provide guidance to regulators, manufacturers and vaccine developers on the manufacturing and the nonclinical and clinical evaluation of respiratory syncytial virus vaccines.² The Guidelines encompass the range of leading technologies currently being assessed at the clinical development stage, namely live-attenuated/chimeric vaccines (including those based on genetically modified organisms), protein-based vaccines (including subunit and particle-based formulations with and without adjuvants) and vaccines produced using recombinant viral and other vector systems. The adoption of the new

¹ An up-to-date list of WHO international biological reference preparations is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 13 March 2020).

² WHO Technical Report Series, No. 1024, Annex 2, 2020.

Guidelines will facilitate the international development, licensure and subsequent prequalification of respiratory syncytial virus vaccines.

29. The Amendment to Annex 3 of WHO Technical Report Series, No. 993, Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated),¹ is a document of strategic importance for global polio eradication. The original Recommendations adopted in 2014 included guidance on the use of several assays that required the use of live poliovirus, and were produced on the basis of limited data and experience with Sabin-based inactivated poliomyelitis vaccines. In addition, there were no specific biocontainment requirements for manufacturing of inactivated poliomyelitis vaccines at that time. Subsequently, the third revision of the WHO 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) was published. The Amendment to the Recommendations issued in 2014 will help to remove a potential bottleneck in the global supply of urgently needed Sabin-based inactivated poliomyelitis vaccines caused by the shortage of high-containment facilities that meet GAPIII requirements.

30. The standardization of biotherapeutics, including similar biotherapeutic products, has been recognized by Member States as an important step in implementing resolution WHA67.21 (2014) on access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy. A request for the revision of the 2009 Guidelines on evaluation of similar biotherapeutic products had been made in an open letter to the Director-General. Following discussion, a second letter was addressed to the Chair of the Expert Committee proposing that the current section 10 of these guidelines, on the clinical evaluation of similar biotherapeutic products, be reviewed and an independent expert consultation organized to discuss in depth the major issues raised, particularly the requirement for clinical trials. The Expert Committee considered that the hypothesis that high-quality data alone would be sufficient to ensure the safety and efficacy of these products was not supported by the information provided. However, it also considered that a more tailored and potentially reduced clinical data package might be acceptable in cases where this was clearly supported by the available scientific evidence. WHO remains strongly committed to increasing access to medicines without compromising their safety and efficacy and the Expert Committee considered that case-by-case flexibility in terms of clinical considerations was already provided for in WHO's current guidance in this area, which was consistent with other national and international regulatory guidance. In line with the above considerations, the Chair of the Expert Committee communicated its conclusions to the Secretariat which indicated that it would evaluate current scientific evidence to support the updating of the 2009 Guidelines.

Implications for the Organization's programmes

31. Several cellular and gene therapy medicines and tissue-engineered products, often referred to as advanced therapy medicinal products, have now been licensed in various parts of the world and several applications submitted to WHO for the assignment of international nonproprietary names. At its seventieth meeting, the Expert Committee established a First WHO International Reference Panel for lentiviral vector copy number and a First WHO International Reference Reagent for lentiviral vector integration site analysis. The Committee believes that setting out the broad principles in this emerging area in a white paper would help to improve patients' access to such products. Such a document could include: (a) a global definition of advanced therapy medicinal products; (b) a strong recommendation that advanced therapy medicinal products must undergo licensing on the basis of data gathered in

¹ WHO Technical Report Series, No. 1024, Annex 3, 2020.

controlled clinical trials; and (c) general remarks on issues to be addressed regarding the quality, safety and efficacy of advanced therapy medicinal products.

32. The Expert Committee noted WHO's Action framework to advance universal access to safe, effective and quality-assured blood products 2020–2023, which is a strategic document intended to guide the work of WHO in the area of blood products and transfusion safety for the next four years. The framework was developed to further promote implementation of resolution WHA63.12 (2010) on the availability, safety and quality of blood products. Based on the analysis of the data collected for WHO's Global database on blood safety in 2015, the framework identifies the major challenges in this area, summarizes WHO's previous responses and establishes six strategic objectives. The framework will serve as a tool for WHO to mobilize donors and technical partners in support of a comprehensive plan of action, and will enable WHO to more effectively fulfil its mandate in this area, thereby increasing the availability of safe, effective and quality-assured blood products in countries. For blood-related issues in general, the Committee acknowledged the contributions and value of WHO's Blood Regulators Network and requested that a draft action plan showing how the network was proposing to operate in future be submitted to it.

33. The Expert Committee on Biological Standardization is WHO's oldest Expert Committee and is tasked with establishing WHO international reference preparations, as well as adopting written standards. Such international reference preparations continue to be developed by collaborative laboratory studies using a variety of assay methods, and following detailed statistical analysis and stability studies. However, both assay technologies and analytical methods have rapidly evolved in line with recent scientific advances. In the 21st century, the Committee is increasingly being requested to develop standards for novel biologicals and diagnostic reagents using ever more sophisticated tools requiring innovative methods of testing, naming and distribution. For example, this year the Committee adopted new international standards in the area of cancer genomics using next-generation sequencing for multiple mutation detection and quantification of tumour DNA, and endorsed a new project to develop reference reagents for the genetic characterization of the human microbiome. The effective standardization of protocols represents the greatest barrier to translational research and product development in the microbiome field. The Committee also approved the addition of 18 reference reagents to the existing WHO reference collection for blood group genotyping, with further such reference reagents certain to be added in future. In these and other evolving fields the Committee will continue to respond to the rapid advances being made in the field of regulatory science.

DRUG DEPENDENCE

Forty-second report of the Expert Committee on Drug Dependence Geneva, 21–25 October 2019¹

34. 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 and make recommendations on whether psychoactive substances should be placed under international control. This mandate is fulfilled through the Expert Committee on Drug Dependence.

¹ WHO Technical Report Series, No. 1026, 2020.

Main recommendations

35. The Expert Committee on Drug Dependence at its forty-second meeting reviewed 13 psychoactive substances and made the following recommendations on substances that should be placed under international control. Four synthetic cannabinoids, three synthetic stimulants, two new fentanyl analogues, two benzodiazepines and one hallucinogen should be placed under international control under either the Single Convention on Narcotic Drugs, 1961 or the Convention on Psychotropic Substances of 1971. Most of these substances have no therapeutic use and have caused or have the potential to cause significant harms to public health, including deaths due to overdose. One synthetic cannabinoid remains under WHO surveillance.

36. The Expert Committee recommended one medicine with marketing authorizations in a few countries, etizolam, be placed under international control owing to evidence of abuse, impaired driving and fatal drug overdose.

37. The Expert Committee also considered reports of abuse of preparations of drugs that are controlled under Schedule III of the Single Convention on Narcotic Drugs, 1961. These include specific preparations of codeine, for which the Committee examined evidence of abuse and dependence and recommended a formal review of these preparations at a future meeting.

Significance for public health policies

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

39. New psychoactive substances such as fentanyl analogues have no therapeutic use and have contributed to substantial numbers of deaths by overdose. The Expert Committee's recommendations would place these substances under international control to restrict their use, and, if adopted by the Commission on Narcotic Drugs,¹ Member States would be requested to implement national control for these substances to comply with the International Conventions.

40. Preparations of codeine have been reportedly abused in different countries across the world, and the Expert Committee will monitor whether current international control measures around these preparations are appropriate to ensure access to them where they are necessary while preventing abuse and dependence and public health harm.

Implications for the Organization's programmes

41. To ensure that psychoactive medicines with proven therapeutic value, such as morphine and other opioids, are available for legitimate use where they are needed, 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 Lists of Essential Medicines. This liaison is to ensure that information is shared on the appropriate use of medicines, including the ones placed under international control, for various conditions, such as the management of pain and palliative care. The Secretariat of the Expert Committee on Drug Dependence also collaborates closely with technical

¹ The recommendations were adopted on 4 March 2020.

departments across the Secretariat to work towards ensuring universal health coverage and that health is central in addressing the world drug problem.

42. The recommendations of the Expert Committee present broad implications for partnership work within WHO's regional and country offices. These include raising awareness of public health risks of psychoactive substances, monitoring drug-related harm through ongoing data collection, and promoting the use of guidelines for improving access to controlled medicines, including those for the management of pain as well as the prevention and treatment of drug use disorders at country level.

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