



Report on meetings of expert committees and study groups¹

Report by the Director-General

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Fifty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations Geneva, 16–20 October 2017²

1. 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 and covers all areas of quality assurance of medicines, from development to distribution to patients.

Main recommendations and outputs

2. For quality control, the Expert Committee adopted 23 new specifications and general texts for inclusion in *The International Pharmacopoeia* and nine International Chemical Reference Substances established by a custodian centre. It endorsed 24 monographs on radiopharmaceuticals developed with the International Atomic Energy Agency. It also endorsed the outcome of WHO's eighth international meeting of world pharmacopoeias (Brasília, 11 and 12 July 2017), hosted by the Brazilian Pharmacopoeia, and adopted two proposed chapters for Good pharmacopoeial practices: on compounding and herbal medicines. The Committee advised continuation of the External Quality Assurance Assessment Scheme for quality control laboratories and adopted the revised text of Considerations for requesting analysis of medicines samples, the Model certificate of analysis (revision) as amended and the WHO Guidance on testing of "suspect" falsified medicines. For manufacturing the Committee adopted WHO guidelines on good herbal processing practices for herbal medicines, Good manufacturing practices (GMP) for herbal medicines and the revised Guidelines for good manufacturing practices for heating, ventilation and air-conditioning systems. Facilitating regulatory synergies, the Expert Committee recommends: Guidance on good practices for desk assessment of compliance with GMP, good laboratory practices and good clinical practices for medical products regulatory decisions; Requirements for stability testing of active pharmaceutical

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. 1010, 2018 (in press).

ingredients and finished pharmaceutical products; and a Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines.

3. The following guidelines were adopted and recommended for use:

- Considerations for requesting analysis of medicines samples (revision);
- WHO model certificate of analysis (revision);
- WHO guidance on testing of “suspect” falsified medicines;
- Good pharmacopoeial practices: Chapter on compounding;
- Good pharmacopoeial practices: Chapter on monographs on herbal medicines;
- WHO guidelines on good herbal processing practices for herbal medicines;
- Good manufacturing practices for herbal medicines (maintenance);
- Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems (revision);
- Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions;
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (revision);
- Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities.

Significance for public health policies

4. The Expert Committee provides a wide spectrum of written and physical standards to enable testing medicines for their quality during their full life cycle from development to distribution to patients. It also recommends regulatory guidelines of importance for 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 quality medicines. Much of the 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 outputs are designed to serve all Member States, especially their national and regional regulatory authorities, organizations in the United Nations system, and regional and interregional harmonization efforts, and they underpin important public health initiatives, including the prequalification and procurement of quality medicines through major international entities, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and UNICEF.

Implications for the Organization's programmes

5. The outcome and recommendations of this Expert Committee have broad implications for the Secretariat's inter- and intra-cluster relationships, links with regional offices, country offices and partnerships, as well as for the work of other WHO expert committees. This Committee's work provides norms and standards for medicines' quality assurance with relevance for all within WHO involved with medicines. The Expert Committee especially serves the Prequalification of Medicines and Regulatory Systems Strengthening teams through the development 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 80 current guidelines and 700 specifications. This Expert Committee provides norms and standards to determine quality for medicines globally and thus assists WHO to fulfil its normative role.

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, 17–26 October 2017¹

Main recommendations

6. The report contains the Expert Committee's evaluations of technical, toxicological, epidemiological, occurrence and dietary exposure data for seven veterinary drug residues (three antimicrobial agents (amoxicillin, ampicillin and halquinol), an acaricide (ethion), an antiparasitic agent (flumethrin), an insecticide (lufenuron) and an anthelmintic (monepantel)). In addition, the Committee considered issues raised by the Codex Committee on Residues of Veterinary Drugs in Foods concerning sisapronil, an ectoparasiticide, and zilpaterol hydrochloride, a β 2-adrenoceptor agonist.

7. The report also presents general considerations and guidance, in particular for chronic dietary exposure assessment of compounds used as veterinary drugs and pesticides and methodological approaches for assessment of antimicrobial residues in food.

8. 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.

9. 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.

¹ WHO Technical Report Series, No. 1008, 2018 (<http://apps.who.int/iris/bitstream/10665/259895/1/9789241210171-eng.pdf>, accessed 7 March 2018).

Significance for public health policies

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

11. 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.

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

13. 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.

14. 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

15. 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 2016–2017: in June and November 2016, and in June and October 2017.

16. 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.

17. 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.

DRUG DEPENDENCE

**Thirty-ninth report of the Expert Committee on Drug Dependence Geneva,
6–10 November 2017¹**

Main recommendations

18. The Expert Committee on Drug Dependence is an independent expert group that evaluates the risks of abuse, dependence, harm to health and the therapeutic usefulness of psychoactive substances. The committee makes evidence-based recommendations to the Commission on Narcotic Drugs for consideration. A total of 16 psychoactive substances were assessed by the Expert Committee at its thirty-ninth meeting.

(a) Recommendations for placement under international control

(i) In Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 as amended by the 1972 Protocol:

- carfentanil

(ii) In Schedule I of the Single Convention on Narcotic Drugs, 1961 as amended by the 1972 Protocol:

- ocfentanyl
- furanyl fentanyl
- acryloylfentanyl
- 4-fluoroisobutyrfentanyl
- tetrahydrofuranyl fentanyl

(iii) In Schedule II of the Convention on Psychotropic Substances (1971)

- AB-CHMINACA
- 5F-ADB/5F-MDMB-PINACA
- AB-PINACA
- UR-144
- 5F-PB-22
- 4-fluoroamphetamine.

¹ WHO Technical Report Series, No. 1009, 2018.

(b) Recommendations for critical review

The Expert Committee recommended that a critical review should be carried out for the following substances at a subsequent meeting of the Expert Committee:

- preparations containing cannabidiol
- pregabalin
- tramadol.

Preparations extracted from the cannabis plant that contain cannabidiol will be reviewed at the 40th Expert Committee on Drug Dependence special session on cannabis (Geneva, 4-8 June 2018).

(c) Recommendations for surveillance

The Expert Committee recommended that etizolam be kept under surveillance owing to the lack of data regarding dependence, abuse, and risks to public health.

Significance for public health policies

19. The substances recommended for scheduling by the Expert Committee were considered to present a substantial risk to public health. Their placement under international control should limit their availability for use and thus reduce the harms to health and save lives.

20. The Expert Committee recommended that several synthetic opioids - primarily analogues of fentanyl that have been associated with a surge in overdose deaths - be placed under international control. The Expert Committee recommended that the fentanyl analogue carfentanil be placed under the most stringent level of international control because of its high potential to cause harm to public health and its ability to produce lethal effects at extremely small doses.

21. The Expert Committee recommended proceeding to a critical review of preparations of cannabidiol. A critical review mandates the Expert Committee to assess evidence of cannabidiol's therapeutic usefulness, abuse and dependence potential, and harm to health, and to issue relevant recommendations for the consideration of the Commission on Narcotic Drugs. That review and the related recommendations of the Expert Committee are expected to have important implications for the use of cannabidiol for medical indications. Current evidence suggests that cannabidiol could have some therapeutic value for seizures caused by epilepsy and related conditions.

Implications for the Organization's programmes

22. In order to ensure that the recommendations of the Expert Committee do not restrict access to essential medicines, it considers the potential for abuse, dependence and harm to health of psychoactive substances alongside their potential for legitimate medical use when issuing its recommendations. The Expert Committee's secretariat works jointly with WHO's Expert Committee on Selection and Use of Essential Medicines which is responsible for updating the WHO Model List of Essential Medicines. This is to ensure that information is shared on the appropriate use of controlled medicines for various conditions, including the management of pain and for palliative care, thus strengthening the evidence base that informs the Expert Committee's recommendations.

23. The recommendations and outcomes of the Expert Committee present broad implications for partnership work within WHO's regional and country offices. This includes raising awareness of public health risks of psychoactive substances, monitoring drug-related harm through ongoing data collection, and promoting the use of guidelines for the prevention and treatment of drug use disorders at country level.

BIOLOGICAL STANDARDIZATION

Sixty-eighth report of the Expert Committee on Biological Standardization Geneva, 17–20 October 2017¹

24. 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 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.

25. 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

26. Based on the results of international collaborative laboratory studies, the Expert Committee established 25 new or replacement WHO international biological reference preparations.² These are the primary standards intended for use as calibrants against which secondary standards (for example, regional or national measurement standards) are benchmarked.

27. The Expert Committee also adopted new guidance documents on:

- the quality, safety and efficacy of Ebola vaccines
- procedures and data requirements for changes to approved biotherapeutic products
- rapid diagnostic tests for HIV infection for professional use and/or self-testing
- establishing stability of *in vitro* diagnostic medical devices.

28. The Expert Committee recommended that WHO urgently establish a small working group of experts to further consider the most appropriate approach and time to develop WHO guidelines for cell therapies and prepare a progress report on this rapidly developing global biologicals field for the Committee's meeting later in 2018. It was also agreed that any WHO standardization activities should include stem cells.

¹ WHO Technical Report Series, No. 1011, 2018.

² WHO Technical Report Series, No. 1011, Annex 6, 2018; for an up-to-date list of WHO international biological reference preparations see <http://www.who.int/bloodproducts/catalogue/en/> (accessed 23 March 2018).

29. 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 2018–2020.

Significance for public health policies

30. A need for specific guidance on the procedures and data requirements for changes to approved biotherapeutic products was identified through a WHO consultation in 2015 as well as by the 16th International Conference of Drug Regulatory Authorities (Rio de Janeiro, Brazil, 26–29 August 2014). The guidelines adopted by the Expert Committee¹ respond to this need and to the request in resolution WHA67.21 (2014) on access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy. The adopted guidelines recommend national regulatory authorities in each Member State to provide regulatory oversight of biotherapeutics including biosimilars throughout their product life-cycle and ensure that only medicines of assured quality, safety and efficacy are available on the market. This new written standard is intended to support Member States in assuring the continued quality, safety and efficacy as well as continuity in supply and access to these highly complex products.

31. The standardization of biological therapeutic medicines was 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).

32. The Expert Committee adopted the first international standard for potency of rituximab, a monoclonal antibody that is used in the treatment of some malignancies, transplant rejection and autoimmune disorders. Rituximab is included on the 19th WHO Model List of Essential Medicines for a basic health-care system.² The use of the international standard should help to harmonize the reporting of bioactivities by different laboratories using their in-house potency assays for various aspects of biological activity.

33. The Expert Committee established the first WHO International Standard and first International Reference Panel for antibodies to Ebola virus. Following the establishment of interim standards in 2015, further work has been conducted to fully evaluate and develop pools of plasma from patients convalescing from Ebola virus disease from countries in Africa, Italy, Norway, the United Kingdom of Great Britain and Northern Ireland, and the United States of America. These reference reagents were developed in response to the Ebola virus disease outbreak in West Africa, which constituted a public health emergency of international concern. They provide stakeholders with internationally validated calibrants with which results generated with neutralization assays in clinical trials can be expressed with a common unit.

¹ WHO Technical Report Series, No. 1011, Annex 3, 2018.

² 19th WHO Model List of Essential Medicines, 2015.
(http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf, accessed 23 March 2018).

Implications for the Organization's programmes

34. Guidelines on the quality, safety and efficacy of Ebola vaccines¹ were prepared in response to the request of the Expert Committee at its sixty-fifth meeting in October 2014 when it recognized the importance of providing guiding principles for evaluation of these vaccines. Development of the guidelines started during the Ebola virus disease outbreak in 2014-2015 and they were reviewed by the Expert Committee at its sixty-seventh meeting in October 2016.² The Expert Committee noted progress in their elaboration but requested further revision to address the potential use of multivalent Ebola vaccines and innovative clinical trial designs. The latest version of the guidelines, adopted by the Expert Committee at its sixty-eighth meeting, includes this new information and also takes note of the fact that the development of Ebola vaccines had been the subject of discussions by the Strategic Advisory Group of Experts on immunization. It is expected that the new written standard for Ebola vaccines will serve as a tool for regulatory preparedness in Member States for future public health emergencies. The adopted text not only provides comprehensive guidance on regulatory expectations for quality, safety and efficacy for full licensure, but also considers which aspects might be accelerated and data sets required during a public health emergency so as to allow rapid vaccine introduction.

35. Technical specifications for rapid diagnostic tests for HIV infection for professional use and/or self-testing³ were defined and included in the document adopted by the Expert Committee in October 2017. The need for these technical specifications was identified in 2015 and has been subject of consultations in 2016 and 2017. The document provides a basis for prequalification of HIV rapid diagnostic tests and should be read in conjunction with the technical specification series and technical guidance series that are provided by prequalification team as instructions for manufacturers of these tests. The Expert Committee was informed on the establishment of a new expert group named the Strategic Advisory Group of Experts on in vitro diagnosis, which will be overseeing some activities related to in vitro diagnosis in future.

36. A technical guidance document on establishing stability of in vitro diagnostic medical devices was prepared in order to improve assessment of the stability of these devices.⁴ The problem was identified by the prequalification team, which observed a lack of appropriate stability studies used by manufacturers without taking into account actual environmental and other conditions for use of products in low- and middle-income countries. The stability of a diagnostic product is essential for its use and considerations provided in this document are intended to ensure stable products in future. For example, details regarding the minimum number of lots that should be tested as well as a need for generating stability of each critical component are expected to be part of regulatory and manufacturers considerations during the development and regulation of these products.

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¹ WHO Technical Report Series, No. 1011, Annex 2, 2018.

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

³ WHO Technical Report Series, No. 1011, Annex 4, 2018.

⁴ WHO Technical Report Series, No. 1011, Annex 5, 2018.