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Report on meetings of expert committees and study groups[1]

Report by the Secretariat

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Forty-ninth Expert Committee on Specifications for Pharmaceutical Preparations Geneva, 13–17 October 2014[2]

1. 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[3]

2. In the area of quality control, the Expert Committee adopted 17 new and revised specifications and general texts for inclusion in *The International Pharmacopoeia*. Furthermore the Expert Committee received the annual report of the custodian centre for International Chemical Reference Substances and adopted 12 International Chemical Reference Substances. It also adopted the revised procedures for the development of specifications for inclusion in *The International Pharmacopoeia* and its section on radiopharmaceuticals.

3. The Expert Committee advised on the report on Phase 5 of the External Quality Assurance Assessment Scheme. The Committee supported the development of the new document on Good Pharmacopoeial Practices, crafted during consecutive international meetings of world pharmacopoeias organized by WHO and hosted by Member States' pharmacopoeias, which aim at convergence of pharmacopoeial requirements.

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[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. 992, 2015.

[3] Detailed recommendations can be found under each relevant section and are summarized in Chapter 15 of the report.

4. The non-sterile process validation included in the guidelines on good manufacturing practices on validation were revised and the newly-elaborated general guidance for inspectors on "hold-time" studies was adopted; the latter is the first such guidance.

5. The Expert Committee endorsed 16 comprehensive technical supplements to complement the existing model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. Moreover, the recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients were updated based on new scientific analytical aspects.

6. The Expert Committee adopted a revision of the guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products together with the revised version of the guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products.

7. A new guideline for national and regional regulatory authorities on good review practice was developed through inter-organizational collaboration and was adopted by the Expert Committee. It is the first set of guidelines of its kind globally and addresses an important gap identified at the International Conference of Drug Regulatory Authorities (Tallinn, 23–26 October 2012).

Significance for public health policies

8. The development and maintenance of written and physical standards to test medicines for their quality, together with a wide range of guidelines, good practices and regulatory guidance in the area of medicines' quality assurance by this Expert Committee, has been a continuing activity since 1947. The outcome and recommendations are designed to serve all Member States, especially their national and regional regulatory authorities, international organizations, the Interagency Pharmaceutical Coordination group and other entities in the United Nations system, regional and interregional harmonization efforts, and underpin important public health initiatives, including the prequalification and procurement of quality medicines through international organizations, such as UNICEF, and major international bodies, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria.

9. The Expert Committee responds to the international need in the area of medicines' quality assurance and the related regulatory fields, including global aspects, risk management, the technical quality aspects in regulatory assessment, inspection, laboratory analysis and supply chain integrity. Much of the work is destined to increase convergence in these areas, and to offer and facilitate efficient synergies among and within the respective authorities.

10. The Expert Committee's deliberations nowadays cover the entire life cycle of medicines from their development to distribution to the patient, wherever he or she may be. The outcome is intended to protect patients and facilitate access to quality medicines.

Implications for the Organization's programmes

11. The outcome and recommendations of the Expert Committee have broad implications within and between clusters, and for links with regional offices, country offices and partnerships. They cover joint topics of interest with the Expert Committees on Biological Standardization and on the Selection and Use of Essential Medicines. In addition, the Committee responds to the needs of major public health interests as identified by other WHO programmes.

12. The Expert Committee's work enables WHO to fulfil its constitutional mandate in this area and has direct or indirect implications for all the WHO programmes and offices that deal with medicines and/or provide advice on medicines' quality. In particular, the Expert Committee serves WHO's regulatory systems strengthening team and the Prequalification Team. The latter could not function without the international guidelines, standards and specifications adopted by this Committee. In return for this service, practical feedback is provided to the Expert Committee through the direct implementation of its more than 80 current guidelines, 700 specifications and 240 International Chemical Reference Substances.

13. Through the Expert Committee's recommendations, WHO is in a position to offer technical scientific advice to all those that deal with the development, production, quality control, regulatory pathways, inspection, supply and procurement of medicines. WHO can provide the tools to help to ensure that quality medicines reach the patients and thus contributes to global health coverage.

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Sixty-fifth report
Geneva, 13–17 October 2014[1]

14. 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

15. 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. Based on the results of international collaborative laboratory studies, the Committee established 12 new or replacement WHO **international biological reference materials**. These are the primary calibrants against which regional or national measurement standards are benchmarked.[2]

16. The Committee also adopted revised written standards for production and control of **inactivated poliovirus vaccines**. New guidelines for **regulatory risk evaluation on finding an adventitious agent in a marketed vaccine** and **procedures and data requirements for changes to approved vaccines** were adopted.

17. The Committee endorsed plans for WHO to support low- and middle-income countries to raise production standards for and regulatory oversight of **blood components and plasma for fractionation**. The plans include formulation of a structured capacity-building programme for qualifying a blood establishment, in parallel with the development and promulgation of national blood

[1] WHO Technical Report Series, No. 993, 2015.

[2] An up-to-date list of WHO International Biological Reference Preparations is available at http://www.who.int/bloodproducts/catalogue/en/ (accessed 23 March 2015).

standards and the implementation of the regulatory oversight considerations. The plans are in line with the resolution WHA63.12 (Availability, safety and quality of blood products), which addresses the need to improve regulatory oversight and quality assurance systems in blood establishments to improve availability, quality and safety of blood products in low- and middle-income countries.

Significance for public health policies

18. Standardization of biologicals has risen to be high on the agenda of Member States (resolution WHA67.21, on Access to biotherapeutic products, including similar biotherapeutic products, and ensuring quality, safety and efficacy). The resolution recognizes that biotherapeutic products have a positive impact on morbidity and mortality rates, but that access to such products has so far been relatively limited, particularly in less-resourced countries but also in well-resourced countries, since some biotherapeutics are very expensive medicines. This situation is likely to change in the near- to mid-term, as more countries start to produce biotherapeutic products. In addition, the expiry of patents and/or data protection for some originator's biotherapeutic products has ushered in an era of "similar" products. The Committee agreed to initiate a review of its standards for biotherapeutic products, including similar biotherapeutic products, and, furthermore, identified a need to define the role of the Expert Committee in the area of advanced therapies, including cell and gene therapy.

19. Under the Global Polio Eradication Initiative countries will be switching from oral polio vaccine to inactivated poliovirus vaccine in order to avoid the reintroduction of poliomyelitis as a result of circulating vaccine-derived polioviruses or vaccine-associated paralytic poliomyelitis. There have been several recent changes in inactivated poliovirus vaccine production and testing, including the use of seed viruses derived from Sabin-strain polioviruses, which have made an update of WHO's previous regulatory guidance necessary. The new guidance will support national regulatory authorities as they make decisions about the licensure of inactivated poliovirus vaccine in support of the priority public health policy to introduce administration of at least one dose of inactivated poliovirus vaccine in national immunization programmes.

20. The finding of an adventitious agent in a biological medicinal product is a major concern to regulatory agencies, manufacturers and public health officials. The most recent examples are the finding of porcine circovirus nucleic acid or infectious circovirus in rotavirus vaccines. In response to such developments, and recognizing the scientific advances made in the detection of adventitious agents in biological medicinal products, the Expert Committee and the International Conference of Drug Regulatory Authorities (Singapore, 30 November–3 December 2010) recommended that WHO take the lead in providing generic guidance to its Member States on this issue. The new WHO guidance therefore outlines the scientific principles of risk evaluation when a signal for a potential adventitious agent or novel endogenous agent is detected in an already licensed or registered vaccine.

21. Changes to the vaccine manufacturing process or product labelling information often need to be made after a new vaccine has been approved by a national regulatory authority. Changes may be made for various reasons, such as to maintain the routine production of vaccines (for example, replenishment of cell banks, seed lots and reference standards), to improve the quality attributes of the vaccine or the efficiency of manufacture (for example, changes in the manufacturing process, equipment or facility), or to update product labelling information (for example, to add a new indication and/or improve the management of risk by adding a warning, limiting the target population, changing the dosage regimen and adding information on co-administration with other vaccines or medicines). If these changes are not managed in a consistent way by regulatory authorities there is a risk of interruption of supply of quality vaccines for immunization programmes. To address this need,

the new WHO standard provides the first-ever guide for establishing national requirements for the regulation of post-approval changes for vaccines.

Implications for the Organization's programmes

22. The Committee provides up-to-date recommendations on the quality, safety and potency of biological substances used in human medicine and ensures the availability of necessary international reference materials. Its work enables WHO to fulfil its constitutional mandate in this area. The global norms and standards defined by the Committee provide the basis for the vaccines prequalification programme to assess the acceptability of vaccines for purchase by PAHO and other international bodies, such as UNICEF.

23. The Committee agreed to form a subgroup of members who will work closely with the Secretariat in order to provide a timely response to the need for standards to support regulation of new interventions against Ebola virus disease. In this context, the recommendations of the WHO Blood Regulators Network on the use of **convalescent plasma or serum in relation to the treatment response to filovirus** set out in a position paper on the collection and use of convalescent plasma or serum as an element in filovirus outbreak response[1] were endorsed by the Committee.

24. The timely development of new WHO reference materials and standards is critically important to harness scientific developments for new biologicals. At the same time, the active management of the existing inventory of reference preparations requires a carefully planned programme of work to replace established materials before the stock of containers, which comprises the standard, is exhausted. The Committee endorsed the initiation of eight new reference preparation projects in order to enable the WHO standards setting programme to continue to deliver appropriate standards at the appropriate time.

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[1] Considerations of the WHO Blood Regulators Network. Potential for use of convalescent plasma in management of Ebola (http://www.who.int/bloodproducts/brn/potential_use_convalescent_plasma_in_management_of_ebola-brn_considerations.pdf?ua=1, accessed 11 March 2015).