

Reports on meetings of expert committees and study groups¹

Report by the Secretariat

BIOLOGICAL STANDARDIZATION

Expert Committee on Biological Standardization

Sixtieth report

Geneva, 19–23 October 2009²

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 to 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. Based on the results of international collaborative laboratory studies, the Committee established 24 new or replacement WHO International Standards or Reference Reagents. These are the primary calibrants against which regional or national measurement standards are benchmarked.³

3. The Committee also adopted revised recommendations to assure the quality, safety and efficacy of both **live attenuated influenza vaccines** and **pneumococcal conjugate vaccines**. A revised version of the new WHO guidelines on the regulatory evaluation of **biotherapeutic products that are similar to existing licensed products** was also adopted.

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. 977, 2013.

³ An up-to-date list of WHO International Standards and Reference Reagents is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 28 February 2013).

Significance for public health policies

4. Recommendations published by WHO provide guidance for national regulatory authorities and manufacturers on production, quality control and associated safety and regulatory issues for biological medicines. These serve as the basis for national regulations. WHO International Standards are used to calibrate regional, national or manufacturers' standards and often form the basis for licensing, routine lot release and clinical dosing worldwide.

5. The continuing development and public health use of influenza vaccines made from live attenuated influenza virus strains made it appropriate to review and update the WHO recommendations for such vaccines. The purpose of the revised recommendations is to provide vaccine manufacturers and national regulatory authorities with guidance on the specific processes for production and control of human, live attenuated influenza vaccines, plus guidance on the nonclinical and clinical evaluation of such vaccines. The successful deployment of live attenuated influenza vaccines depends on ensuring an appropriate balance between attenuation and immunogenicity. Knowledge of the genetic markers associated with virus attenuation has increased, allowing more stringent control of the vaccine. The aim is to produce an attenuated virus that incorporates the key immunizing antigens and antigenic determinants of circulating wild influenzaviruses but retains the stable genetic and phenotypic characteristics of the attenuated donor strain when given to susceptible individuals on a wide scale. Additionally, considerable efforts have been devoted to pandemic planning to ensure that safe and effective vaccines can be produced quickly in response to a pandemic emergency.

6. Infections caused by *Streptococcus pneumoniae* are responsible for substantial morbidity and mortality, particularly in very young and elderly subjects. The development of pneumococcal conjugate vaccines, in which each of the selected bacterial capsular polysaccharides is coupled to a protein carrier molecule, has been a major advance in the prevention of invasive pneumococcal disease. Since 2006, WHO has recommended that all countries incorporate pneumococcal conjugate vaccines in routine immunization schedules for children aged less than two years with priority being given to their introduction in countries with high child mortality rates and/or high rates of HIV infection. WHO's recommendations for pneumococcal conjugate vaccine production and control were first established in 2003. The Expert Committee adopted a revised document that had been developed to take into account the most recent developments in the field. In particular, the recommendations provide guidance on the design of immunogenicity studies that should be performed in order to support the licensure of new pneumococcal conjugate vaccines (including those containing conjugated capsular polysaccharides of serotypes additional to or different from those in already licensed vaccines). These steps will facilitate regulatory evaluation of second-generation vaccines and contribute to increased access to these vaccines.

7. Although biotherapeutic products have a successful record in treating many life-threatening and chronic diseases, patients have limited access to such medicines, particularly in developing countries. The expiration of patents and/or of data protection for the first major group of innovative biotherapeutics is ushering in an era of products "similar" to the originals, with the potential significantly to enhance accessibility. The guidance adopted by the Committee on appropriate regulation of this new class of products has been developed in response to requests by many developing countries.

Implications for the Organization's programmes

8. 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 assessing the acceptability of vaccines for purchase by the PAHO Revolving Fund and other international bodies, such as UNICEF.

9. The Committee's observations, conclusions and recommendations have significant implications for several of WHO's activities. In particular, they provide recommendations and reference preparations for assuring the quality, safety and efficacy of vaccines and blood products, and the provision of reference materials for standardizing essential diagnostic assays for the detection of contaminants in blood products.

10. The Committee established several important new WHO International Standards, Reference Reagents and, in order to meet modern regulatory needs, a Reference Panel aimed at improving detection of blood-borne infectious agents and other infectious diseases. The First International Reference Panel for hepatitis B virus, covering the most prevalent genotypes (A–G) worldwide, will facilitate the detection of relevant genotypes by all countries as well as improvement of the quality of hepatitis B diagnostic devices. Of similar importance, the First International Standard for detection of HIV-2 RNA in nucleic acid amplification technologies constitutes a major step advance in the detection of the HIV-2 group of viruses and improvement in the quality of diagnostic tests. Furthermore, the International Standards for essential medicines, such as heparin and blood coagulation factor VIII or diagnostic reagents such as thromboplastin for the control of anticoagulant therapy, underpin their medical application and the regulation of blood products and in vitro diagnostic devices at the global level.

11. The chairman of the WHO Blood Regulators Network reported to the Committee on the activities of the Network that linked six control and regulatory authorities. Its objectives are to serve as an expert group in the blood field, share expertise and information, move towards a convergent regulatory policy, and seek solutions to emerging public health challenges. The Network's members reviewed a tool that will enable WHO to assess national blood regulatory systems.

Expert Committee on Biological Standardization¹

Sixty-first report

Geneva, 18–22 October 2010²

Main recommendations

12. 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 16 new or replacement WHO International Standards or

¹ See paragraph 1 for explanation of its purpose.

² WHO Technical Report Series, No. 978, 2013.

Reference Reagents. These are the primary calibrants against which regional or national measurement standards are benchmarked.¹

13. The Committee also adopted revised written standards for production and control of **live attenuated yellow fever vaccines** and revised recommendations for the production and control of **recombinant hepatitis B vaccines** and for **evaluation of animal-cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks**. New WHO guidelines on the **independent lot release of vaccines by regulatory authorities** were adopted. The Committee also adopted a revision to the **procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies**. In collaboration with the Expert Committee on Specifications for Pharmaceutical Preparations, the Committee adopted WHO guidelines on **good manufacturing practices for blood establishments** and for the **storage and transport of time- and temperature-sensitive pharmaceutical products**.

Significance for public health policies²

14. Cell substrates – the cells used to manufacture a biological product – and events linked to cell growth can affect the characteristics and safety of the resultant biological products. Therefore, a thorough understanding of the characteristics of the cell substrate is essential in order to identify points of concern and to develop a quality-control system that meets those concerns. The recommendations adopted by the Committee provide guidance to national regulatory authorities, national control laboratories and manufacturers on basic principles and, in some cases, detailed procedures that are appropriate to consider in the characterization of animal cells that are proposed for use in the manufacture of biological products.

15. Vaccine lot release conducted by regulatory authorities is part of the regulation of vaccines and involves the independent assessment of each individual lot of a licensed vaccine before it is released onto the market. This assessment is based, as a minimum, on the review of manufacturers' summary protocols. It may be supplemented, in some circumstances, by independent testing that is independent of the manufacturers' quality-control testing. WHO provides support for lot-release programmes, through provision of written and measurement standards, strengthening the lot-release function of national regulatory authorities and providing training. The guidelines adopted by the Committee provide recommendations and strategies for lot release of vaccines by the national authorities of producing and procuring countries.

16. WHO provides a prequalification service to ensure that vaccines provided through the United Nations for use in national immunization services in different countries are safe, effective and suitable for the target populations, at the recommended immunization schedules and with appropriate concomitant products. The procedure in place at WHO was last revised in 2005. The Committee adopted a revision that takes into consideration challenges faced by the vaccines prequalification programme, such as the increasing number of submissions and the increasing diversity and complexity of the products submitted to WHO for evaluation, as well as the maintenance of the prequalified status for those vaccines on the list. The latter includes reassessments and reviews of variations, and investigation of quality and safety concerns reported by fieldworkers.

¹ An up-to-date list of WHO International Standards and Reference Materials is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 28 February 2013).

² See paragraph 4 for general information.

17. The importance of establishing reliable quality-assurance systems covering the whole chain from blood collection, processing and distribution of blood components in blood establishments is emphasized in resolution WHA63.12 on availability, safety and quality of blood products, as a necessary measure that would contribute to increase the global availability of plasma that meets internationally recognized standards. The Expert Committee adopted current, widely accepted principles of good manufacturing practices that are relevant to the consistent production of safe and good-quality blood components in blood establishments, including related donor-safety issues. It is intended to serve as a guidance document for both blood establishments and national regulatory authorities when implementing and enforcing these concepts.

Implications for the Organization's programmes

18. The general implications are set out in paragraph 8 above.

19. The Chairman of the WHO Blood Regulators Network reported to the Committee on recent activities of the Network, including reviewing the draft document describing the development of assessment criteria for national blood regulatory systems, and technical support and advocacy for implementing resolution WHA63.12 on availability, quality and safety of blood products.

20. The Committee also recommended that WHO convene implementation workshops for selected newly established written standards. In particular, attention should be paid to the evaluation of animal-cell cultures as substrates for the manufacture of biological medicinal products and to the guidelines on the lot release of vaccines. The revised procedure for prequalification of vaccines also requires substantial follow-up to ensure a good understanding, particularly by vaccine manufacturers.

Expert Committee on Biological Standardization Sixty-second report Geneva, 17–21 October 2011¹

Main recommendations²

21. Based on the results of international collaborative laboratory studies, the Committee established 15 new or replacement WHO International Standards or Reference Reagents. These are the primary calibrants against which regional or national measurement standards are benchmarked.³

22. The Committee adopted revised recommendations for assuring the quality, safety and efficacy of **BCG vaccines** and **acellular pertussis vaccines**. It also adopted revised WHO guidelines on the regulatory evaluation of **live, attenuated dengue tetravalent vaccines** as well as a generic protocol for the **calibration of seasonal and pandemic influenza antigen working reagents** by WHO Essential Regulatory Laboratories. Revised guidelines for **thromboplastins and plasma** used to control oral anticoagulant therapy with vitamin K antagonists and assessment criteria for **national blood regulatory systems** were also adopted.

¹ WHO Technical Report Series, No. 979, 2013.

² See also paragraph 2 above.

³ An up-to-date list of WHO International Standards and Reference Reagents is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 28 February 2013).

Significance for public health policies¹

23. In 1993 WHO declared tuberculosis a public health emergency, and *Mycobacterium tuberculosis* is now considered to be responsible for more adult deaths than any other pathogen. Vaccination with the BCG vaccine remains the standard for tuberculosis prevention in most countries because of its efficacy in preventing life-threatening forms of the disease in infants and young children. It is inexpensive and usually requires only one administration in either neonates or adolescents. As there is currently no suitable alternative, BCG will remain in use in the foreseeable future and may continue to be used as a prime vaccine in a prime-boost immunization schedule in conjunction with new tuberculosis vaccines. The last revision of the WHO requirements for BCG vaccine for human use was in 1985. Recent WHO consultations have considered the issue of improving BCG vaccine characterization and quality-control assays so as to reflect current state-of-the-art technology. In addition, the international reference preparation for BCG vaccine has been replaced by sub-strain specific reference reagents evaluated by multi-country collaborative studies. The Expert Committee recommended that the updated guidance be adopted so that modern specifications are applied to assure the safety and efficacy of BCG vaccines.

24. Pertussis immunization is an integral part of immunization programmes in all regions of the world. It is recommended for all infants and children and in some countries also for adults and adolescents. Whole-cell pertussis vaccines have been used for more than 50 years, have been shown to provide protection, and are still the foundation of global pertussis control. However, there is increasing interest in acellular pertussis vaccines, which have also been shown to be safe and effective and which have been successfully introduced into many national immunization programmes. As a consequence of increasing demand for acellular pertussis vaccines, new manufacturers are entering the field. The expansion in the number and use of acellular pertussis vaccines, the development of new vaccines and advances in the standardization of quality-control methods have prompted WHO to update the current WHO guidelines (established in 1998) for the production and control of the acellular pertussis component of monovalent or combined vaccines. The Expert Committee recommended the adoption of revised WHO guidance for improving the quality control of existing vaccines on the basis of new information and experience, and for evaluating new products and new combinations through manufacturing control and through both nonclinical and clinical studies.

25. Reagents for assessing the potency of influenza vaccines are prepared annually as the strains in the vaccine are updated. The calibration process involves independent evaluation by the four WHO Essential Regulatory Laboratories. In order to make this process more transparent, a generic protocol that describes in detail the process by which the four Laboratories develop and calibrate the reagents had been prepared. After making suitable amendments, the Committee recommended that the generic protocol be adopted by WHO.

26. Oral anticoagulant medicines are widely used in the treatment and prophylaxis of thrombotic disorders. For each patient, the dose of these medicines must be adjusted periodically in order to ensure an adequate, but not excessive, degree of anticoagulation. The adjustments are made on the basis of the results of the prothrombin-time or similar test on the patient's blood. The test is regulated by the use of calibrated thromboplastins and plasmas. An International Normalized Ratio/International Sensitivity Index system is used for this purpose. The establishment and maintenance of this system are defined in WHO's guidelines. The Committee recommended the adoption of revised guidelines that provide more information on the preparation, certification and use of certified plasmas for

¹ See also paragraph 4 above.

International Sensitivity Index calibration and International Normalized Ratio determination. The criteria to apply in the choice of thromboplastin reagents were also provided.

Implications for the Organization's programmes¹

27. Assessment criteria for national blood regulatory systems were also adopted by the Committee. These provide a new tool for evaluating national regulatory authorities in relation to the regulation of blood, blood components, plasma-derived products, and associated substances and medical devices including in vitro diagnostics. The assessment criteria are designed to identify shortcomings to be overcome by future development, thus strengthening the regulatory oversight of national regulatory authorities. It is expected that the tool will help to identify priorities based upon which capacity-building programmes could be developed to support the introduction of blood-products regulation and to sustain implementation of resolution WHA63.12 on availability, quality and safety of blood products. The Committee highlighted the need for WHO to develop an implementation plan, including guidance on the correct use of the tool, as part of the capacity-building activities requested in resolution WHA63.12.

EVALUATION OF CERTAIN FOOD ADDITIVES

Joint FAO/WHO Expert Committee on Food Additives Seventy-sixth report Geneva, 5–14 June 2012²

Main recommendations

28. The Committee evaluated the safety of five food additives and 12 groups of flavouring agents, and established acceptable daily intake values or issued other safety statements. Specifications for the following food additives were revised: ethyl cellulose, mineral oil (medium viscosity), modified starches and titanium dioxide.

29. The report also contains general considerations and guidance, in particular on adequate and timely submission of data so as to allow complete evaluation, and recommendations for future work by the Committee and further research.

30. The Committee's assessments, recommendations and comments will be discussed by the Codex Committee on Food Additives in order to provide recommendations for the safe use of these food additives to national authorities and to identify and recommend appropriate risk management and risk-mitigation measures to reduce human exposure, where necessary.

31. WHO has published detailed monographs of the toxicological and other related information upon which the safety assessments of the compounds were made³ and FAO published summaries of the identity and purity of food additives.⁴

¹ See also paragraphs 8 and 9.

² WHO Technical Report Series, No. 974, 2012.

³ WHO Food Additive Series No. 67, 2012.

⁴ Food and Agriculture Organization of the United Nations. *Compendium of food additive specifications*. Joint FAO/WHO Expert Committee on Food Additives, 76th meeting, 2012, JECFA Monographs 13, FAO, 2012.

Significance for public health policies

32. The Committee's work identifies, and if possible quantifies, the public health significance of exposure to food additives and contaminants through an international consensus scientific risk assessment. If a health concern is identified, clear recommendations are given for action by national governments or through the Codex Alimentarius Commission and its subsidiary bodies.

33. Although all Member States face the problem of assessing potential risks of chemicals in food, only a few scientific institutions, on a national or regional basis, systematically assess all relevant toxicological, epidemiological and related data. Therefore it is important to provide Member States with valid information on both the general aspects of risk assessment and specific evaluations of the food additives covered in this report. The Committee's work, in its complexity and in reaching an international consensus in the evaluation of these compounds, is unique in its importance and impact on global public health decisions related to food safety.

34. The Committee's recommendations are used by the Codex Alimentarius Commission for setting international food safety standards and other guidance and recommendations. Such standards are established only for substances that have been evaluated by the Joint Committee. This process ensures that food commodities in international trade meet strict safety standards.

35. The advice provided by the Committee is also considered by Member States directly when setting national or regional food safety standards.

Implications for the Organization's programmes

36. The evaluation of chemicals in food by the Committee is a continuing activity. Three meetings of the Joint FAO/WHO Expert Committee on Food Additives were planned for the biennium 2012–2013: one was held in June 2012 on food additives and contaminants, another is scheduled to be held in June 2013 on food additives and contaminants, and a third meeting on evaluating residues of veterinary drugs in food is due to be held in November 2013.

37. WHO is a partner in the Joint FAO/WHO Food Standards Programme, whose principal organ is the Codex Alimentarius Commission, for whose activities the Committee's work is crucial. International standards and recommendations on food additives and contaminants in food elaborated by the Commission are based on the work of the Joint FAO/WHO Expert Committee on Food Additives.

38. Regional offices and WHO Representatives also make use of the Committee's evaluations when advising Member States on food safety issues.

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Expert Committee on Specifications for Pharmaceutical Preparations

Forty-seventh report

Geneva, 9–12 October 2012¹

Main recommendations

39. The Expert Committee on Specifications for Pharmaceutical Preparations reviews developments and advises the Director-General and Member States in the area of quality assurance of medicines. It provides recommendations and tools to assure the quality of medicines throughout their life-cycle from development to final distribution to patients, including international supply mechanisms. Detailed recommendations can be found under each relevant section in the report.

40. The Expert Committee adopted 26 new monographs and general texts for inclusion in *The International Pharmacopoeia*. The specifications under development are internationally applicable test methodologies for anti-infective, antimalarial, antituberculosis, and antiretroviral medicines, as well as medicines for children and contraceptives. In addition, eight new International Chemical Reference Substances were adopted for use in testing medicines. The Expert Committee members also adopted an updated release procedure for International Chemical Reference Substances in order to render more efficient the establishment of these physical standards.

41. In view of the analytical challenges faced when testing antimalarial medicines including artemisinin derivatives, the Expert Committee updated the recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients, and the related test specifications for finished pharmaceutical products, reflecting new scientific findings based on studies done with WHO collaborating centres.

42. The Committee newly adopted a WHO guideline on quality risk management for assisting regulatory authorities in improving control of medicines by increasing the effectiveness of their activities within the limits of available resources, through the assessment of individual risks related to finished products and starting materials and the recognition of hazards at specific stages of production or distribution.

43. In order to support the work of the United Nations Prequalification of Medicines Programme managed by WHO, the Expert Committee updated the guidance on variations to a prequalified product. Moreover, it adopted a new collaborative procedure between the Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products with a view to facilitating the exchange of information between WHO and national medicines regulatory authorities and to avoid duplication of work.

44. The Expert Committee strongly recommended the continuation of the External Quality Assurance Assessment Scheme for the quality control of laboratories with the involvement of WHO regional offices, in order to enable participating laboratories to improve their performance.

¹ WHO Technical Report Series, No. 981, 2013.

45. The Expert Committee furthermore expressed its support for the WHO initiative in the area of providing a platform towards future convergence of pharmacopoeial requirements in close collaboration with the world pharmacopoeias.

Significance for public health policies

46. WHO's international guidelines, and physical standards developed under the aegis of this Expert Committee for more than 60 years, are designed to serve all Member States, international organizations, and organizations in the United Nations system, to support regional and interregional harmonization efforts, and to underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, Stop TB, essential medicines and medicines for children.

47. The advice and recommendations provided by the Expert Committee are intended to protect patients by providing support to Member States, procurement agencies, major international bodies and institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations and bodies such as UNICEF, in their efforts to provide good-quality medicines to those who need them.

48. The Expert Committee responds to new scientific trends and the increasing complex international supply chains as, for most countries, the processes associated with the manufacture of starting materials and finished products have shifted beyond their borders, thereby resulting in more complex regulatory processes that have acquired an international dimension.

Implications for the Organization's programmes

49. The Expert Committee provides up-to-date recommendations on the quality of pharmaceutical starting materials, such as active pharmaceutical ingredients, excipients and finished products and ensures the availability of necessary international reference materials. Its work enables WHO to fulfil its constitutional mandate in this area.

50. The Expert Committee's observations, conclusions and recommendations have significant implications for several of WHO's activities and programmes within the Organization, as they provide timely up-to-date standards and guidance in the area of quality assurance of medicines, recommendations and reference standards for assuring the quality medicines.

51. The Expert Committee especially serves the Prequalification of Medicines Programme managed and operated by WHO, as this could not function without the international guidelines, standards and specifications adopted by the Committee. A significant advantage is that, as a result of the immediate implementation of those guidelines and specifications, practical feedback for clarification, and potential revision or the need for additional guidance are communicated to the Expert Committee.

52. Based on the Expert Committee's recommendations, WHO is in a position to provide technical support to the Organization as well as to relevant external bodies dealing with the supply and procurement of medicines, in providing tools that will help to ensure the safety, efficacy and quality of medicines for maintaining and improving public health within the global health coverage.

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