

Reports of advisory bodies

Expert committees and study groups¹

Report by the Secretariat

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Sixty-third report Geneva, 15–19 October 2012²

1. The Expert Committee 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.

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.

Main recommendations

3. Based on the results of international collaborative laboratory studies, the Committee established 19 new or replacement international reference materials. These are the primary calibrants against which regional or national measurement standards are benchmarked.³

4. The Committee also adopted revised written specifications for the quality, safety and efficacy of **oral poliomyelitis vaccine (OPV); diphtheria vaccines; tetanus vaccines; combined diphtheria-, tetanus- and pertussis-containing vaccines; and Japanese encephalitis vaccines (live, attenuated)**. New WHO guidelines for regulatory evaluation of **malaria vaccines** were 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. 980, 2013.

³ An up-to-date list of WHO International Biological Reference Preparations is available at <http://www.who.int/bloodproducts/catalogue/en/> (accessed 24 October 2013).

Significance for public-health policies

5. 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. They serve as the basis for national regulations. WHO International Standards are used for calibrating regional, national or manufacturers' standards and often form the basis for licensing, routine lot release and dose determination worldwide.

6. Progress in the control (and, since 1988, eradication) of poliomyelitis has been due mainly to widespread use of vaccines. In addition to trivalent oral poliomyelitis vaccine (OPV, which is used in many countries for routine or supplementary vaccination), monovalent OPVs against type 1 (mOPV1) and type 3 polioviruses (mOPV3) and bivalent OPV against types 1 and 3 (bOPV, used in the Global Polio Eradication Initiative) have been licensed for use in countries where types 1 and 3 are endemic or for outbreak control in situations where one or two types can re-emerge. Monovalent OPV against type 2 poliovirus has been licensed, but is expected to be stockpiled for use in response to emergencies. Recently, the Director-General asked the Strategic Advisory Group of Experts on immunization to consider the possible replacement of tOPV by bOPV for routine immunization globally. WHO Recommendations for production and control of OPV were last revised in full in 1999. Since then scientific knowledge has advanced, novel laboratory techniques have become available for evaluation of OPVs, and new formulations such as the monovalent and bivalent vaccines are in use. The revised Recommendations incorporate these developments and the Committee agreed that they be adopted.

7. Combined vaccines that allow simultaneous administration of diphtheria (D) and tetanus (T) toxoids with several other antigens have been in use since the middle of the 20th century. Some of the earliest DT-based combined vaccines included inactivated polioviruses and/or whole-cell pertussis products (DTwP). These were followed by combinations containing various acellular pertussis antigens (DTaP) as an alternative to DTwP and the addition of one or more *Haemophilus influenzae* type b conjugate and hepatitis B surface antigen. Currently there are many DTwP-based and DTaP-based combined vaccines available worldwide that vary in the amounts of each antigen and the total range of antigens according to the intended age range for use (i.e. infants, children, adolescents and adults). The first WHO Requirements for diphtheria, tetanus, pertussis and combined vaccines were published in 1990. Subsequent scientific and regulatory advances have necessitated an update to this guidance. Revised Recommendations for DT-based combined vaccines were considered by the Committee, which agreed that they be adopted.

8. The Committee adopted new guidelines that are intended to provide guidance to national regulatory authorities and vaccine manufacturers on the quality (including production, quality control, characterization, and stability), nonclinical and clinical aspects of recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of *Plasmodium falciparum*. Various approaches are being used to develop malaria vaccines, with different production platforms and target stages of the plasmodial life cycle. At the time of development of these guidelines only one candidate vaccine, a recombinant *P. falciparum* malaria vaccine produced in yeast that targets the pre-erythrocytic stage, was currently under evaluation in Phase III clinical trials. Additional and specific considerations are necessary for clinical development of transmission-blocking malaria vaccines because these are intended for the reduction of malaria transmission by stopping or interfering with the sexual stage of the parasite's life cycle, and are not expected to prevent malaria disease directly in vaccinated individuals.

Implications for the Organization's programmes

9. 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 PAHO and other international bodies, such as UNICEF.

10. 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.

11. In resolution WHA63.12 on availability, safety and quality of blood products, adopted in 2010, the Health Assembly recognized the need to improve access to safe blood products globally. One of WHO's main activities in this field is to provide support to low- and middle-income countries so as to enable them to prepare recovered plasma for fractionation with the aim of producing essential plasma-derived medicines (such as blood coagulation factors and polyvalent and specific immunoglobulins) for their populations. The amount of plasma wasted in low- and middle-income countries is estimated to be about 9.3 million litres of non-transfused plasma annually. Key elements that will affect future plasma-recovery efforts include ensuring governmental commitment to establishing domestic processes, a favourable cost-benefit analysis, securing the necessary investment, the existence of a strategy for managing the residual health risks associated with recovered plasma, organizing national blood services to include regulatory oversight of blood establishments, and implementation and enforcement of good manufacturing practices. To facilitate the implementation of resolution WHA63.12, the Committee proposed that WHO: prepare guidance on estimating the residual health risk in blood components, including plasma for fractionation; issue guidelines, advocacy information or both for determining the utility of plasma contract fractionation or local production in Member States; and include blood and blood components in the WHO Model List of Essential Medicines.

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Seventy-seventh Joint FAO/WHO Expert Committee on Food Additives Rome, 4–13 June 2013¹

Main recommendations

12. The Committee assessed, and reached conclusions on, the safety of seven food additives and reviewed dietary exposure to cadmium from cocoa and cocoa products. Acceptable daily intake values or other safety statements were established. Specifications for 17 food additives were revised.

13. The report also contains general considerations and guidance, in particular on analytical methods for food additives and the new food consumption data compiled in the Global Environment Monitoring System/Food and to be used in dietary exposure assessments.

¹ WHO Technical Report Series, No. 983, 2013, in press.

14. The Committee's assessments, recommendations and comments will be discussed by the Codex Committee on Food Additives and the Codex Committee on Contaminants in Food in order to provide Codex 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.

15. WHO has published detailed monographs of the toxicological and other related information upon which the safety assessments of the compounds were made¹ and FAO has published summaries of the identity and purity of food additives.²

Significance for public health policies

16. 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, and provides guidance of the safe use of food additives. If a health concern is identified, clear recommendations are given for action by national governments or through the Joint FAO/WHO Food Standards Programme (i.e. the Codex Alimentarius Commission and its subsidiary bodies).

17. 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 that Member States are provided with valid information on both the general aspects of risk assessment and specific evaluations of 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.

18. The Committee's recommendations are used by the Codex Alimentarius Commission for setting international food safety standards and issuing other guidance and recommendations. Such standards are science-based and are established only for substances that have been evaluated by the Committee, thereby ensuring that food commodities in international trade meet strict safety standards in order to protect the health of the consumer and ensure fair practices in food trade.

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

Implications for the Organization's programmes

20. The evaluation of chemicals in food by the Committee is an ongoing activity. Three meetings of the Joint FAO/WHO Expert Committee on Food Additives were planned for 2012–2013: two were held in June 2012 and June 2013 on food additives and contaminants, and the third was held on 5–14 November 2013 to evaluate residues of veterinary drugs in food.

21. The Committee's work is crucial for the work of the Codex Alimentarius Commission in assuring the sound scientific base for international standards and recommendations on food additives and contaminants in food, developed by the Commission on the basis of the work of the Committee.

¹ Safety evaluation of certain food additives. WHO Food Additives Series No. 68, 2013, in press.

² Compendium of food additive specifications. FAO JECFA Monographs 14, 2013, in press.

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

SELECTION AND USE OF ESSENTIAL MEDICINES

19th meeting the Expert Committee on the Selection and Use of Essential Medicines Geneva, 8–12 April 2013¹

23. The Expert Committee met in order to update the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children.

Main recommendations

24. The Committee recommended renaming Section 2 in both Model Lists as “Medicines for Pain and Palliative Care” in order to recognize the importance of palliative care in not only cancer but also in conditions such as HIV/AIDS, multidrug-resistant tuberculosis and severe congenital diseases. Furthermore, medicines needed for the treatment of other common symptoms in palliative care such as anorexia, nausea, constipation and diarrhoea were also included in Section 2.

25. The Committee reviewed the evidence and added pegylated interferon alpha (2a or 2b) (in combination with ribavirin) for obtaining a sustainable virological response in the treatment of hepatitis C to the 18th WHO Model List of Essential Medicines. The Committee also noted the high level of expertise and specialized facilities needed for safe and effective use of interferons and the high cost of this treatment. It therefore included pegylated interferon plus ribavirin in the Complementary List of the 18th WHO Model List of Essential Medicines.

26. The Committee reviewed the applications for deletion of oseltamivir and decided to retain it on both Model Lists with the restricted indication of potentially severe or complicated illness due to confirmed or suspected influenza virus infection, in accordance with WHO's treatment guidelines.

27. An urgent review of Section 8.2 (Cytotoxic and adjuvant medicines) was recommended by the Committee. It noted the strong evidence in support of the applications for inclusion of imatinib and trastuzumab but deferred a decision until the review was completed.

28. Bevacizumab was added to the Complementary List in the 18th Model List of Essential Medicines for neovascular age-related macular degeneration; the Committee noted that the evidence for the efficacy of bevacizumab in this condition was from two large publicly funded trials. It also noted the precautions necessary for safe intravitreal use of bevacizumab.

29. The Committee added risperidone as an alternative to chlorpromazine and haloperidol; it added clozapine to the Complementary List of the 18th Model List of Essential Medicines for individuals with psychosis not responding to other antipsychotic medicines.

30. Chlorhexidine (7.1% solution or gel delivering 4%) was added to the Core List of both Model Lists by the Committee for use in umbilical cord care in community settings. The product would help to decrease neonatal mortality and omphalitis in home births.

¹ WHO Technical Report Series, in preparation.

31. Other medicines that were added to the 17th Model List were loratidine, loperamide (for adults only in the context of palliative care), hyoscine butyl bromide, gliclazide (to replace glibenclamide), latanoprost eye drops and to both lists, ofloxacin eye drops, hydromorphone, oxycodone, fomepizole and prothianamide.

32. In addition, the Committee recommended that whole blood and erythrocytes should be added to the Core List in both Model Lists in view of their importance for the treatment of haemorrhage. The Committee requested that its strong support of the principle that blood should be obtained exclusively from voluntary non-remunerated donors be noted in conjunction with the listing of whole blood and erythrocytes in the Model Lists.

33. The Committee also emphasized that, given the increasing number of applications, the limited time available at its meetings and the need to coordinate with the development of WHO's guidelines, a greater frequency of meetings and alternative forums such as virtual meetings are required in order for it to respond in a timely manner to new clinical developments.

Significance for public health policies

34. The WHO Model List of Essential Medicines provides guidance to Member States for making evidence-informed national decisions and prioritizing the supply and use of medicines to meet most of their domestic health needs.

35. With the addition to the List of pegylated interferons, a treatment for hepatitis C is now covered by the Model List; however, as newer treatments such as protease inhibitors are becoming available, they will need to be reviewed.

36. The inclusion of bevacizumab would provide an effective treatment for neovascular age-related macular degeneration in elderly people.

37. Inclusion of risperidone and clozapine would provide a wider choice of treatments for schizophrenia.

Implications for the Organization's programmes

38. Continued updating of the Model Lists provides Member States, other United Nations bodies, the Secretariat and nongovernmental organizations with a critical tool for use in the selection, procurement and use of medicines.

39. The review and use of evidence, as well as the Committee's transparent way of working, offer a model for countries in achieving the optimal selection and use of medicines. The Secretariat communicates to countries the changes made to the Model Lists and works with countries upon their request in updating their National Essential Medicines List and strengthening their selection processes.

HUMAN AFRICAN TRYPANOSOMIASIS CONTROL AND SURVEILLANCE¹

Meeting of the Expert Committee on Control and Surveillance of Human African Trypanosomiasis Geneva, 22–26 April 2013²

40. The Expert Committee met to consider information about new diagnostic approaches, new therapeutic regimens and the better understanding of the distribution of human African trypanosomiasis provided by high-quality mapping. The roles of human and animal reservoirs and the tsetse fly vectors were emphasized. The Committee reviewed and updated control and surveillance methods in view of the objective of eliminating human African trypanosomiasis, as set out in the WHO's roadmap to accelerate the work to overcome the global impact of neglected tropical diseases, which was noted by the Health Assembly in resolution WHA66.12.³

Main recommendations

41. The Committee recognized that the goal of elimination of the gambiense form of the disease was feasible. The Committee highlighted the importance of the contributions from both the public and private sectors to the improvement of the situation, and recommended that advanced tools be developed as a means to realize elimination.

42. Concerning the epidemiology of the disease, the Committee recommended that surveillance and control of human rhodesiense trypanosomiasis must be coordinated with veterinary services in a "One Health" approach, particularly in areas of potential overlap with the gambiense form of the disease.

43. As regards screening, diagnostics and follow-up, the Committee decided that the card agglutination test for trypanosomiasis continues to be recommended for use in active screening of *Trypanosoma brucei gambiense* infection. For passive screening of *T. b. gambiense* infection, individual rapid diagnostic tests are recommended. Systematic follow-up after treatment is no longer recommended. Follow-up, including examination of cerebrospinal fluid, should be confined to patients with clinical features suggestive of relapse. In the special case of clinical trials, post-treatment follow-up with regular control visits remains mandatory. The recommendations for clinical trials of treatment of human African trypanosomiasis should be revised. Molecular methods should not be used for making therapeutic decisions.

44. Treatment needs safe, and if possible oral, medicines that are active against both disease forms and easy to use. The Committee strongly encouraged research on such agents. It recommended that melarsoprol should not be used as a first-line treatment for the second stage of *T. b. gambiense* infections. The treatment of choice should be nifurtimox and eflornithine combination therapy, which is already included in the WHO Model List of Essential Medicines.

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. 984, 2013, in press.

³ Document WHO/HTM/NTD/2012.1.

45. The Committee stressed the role of vector control as complementary to medical approaches to tackling human African trypanosomiasis in an integrated strategy for the elimination of gambiense disease and the control of rhodesiense disease.

46. The Committee recommended exploration of the epidemiological roles of people with parasitologically unconfirmed, serologically suspected African trypanosomiasis and of animals as reservoirs of *T. b. gambiense*. It recommended that operational research is needed to integrate human African trypanosomiasis into existing health systems and to optimize passive case detection, surveillance and management of disease in these systems. Human resource capacity should be enhanced in all areas of control of human African trypanosomiasis, including case detection, patient care, vector control, programme management and operational research.

Significance for public health policies

47. The Committee's recommendations provide guidance for national health authorities on how to use new tools available for screening populations at risk of human African trypanosomiasis. The card agglutination test for trypanosomiasis must be used only for mass screening by mobile teams in villages in areas endemic for the disease whereas individual rapid diagnostics tests are mainly reserved for use in passive screening in fixed health care facilities.

48. Diagnostic algorithms could be affected by the Committee's recommendation that diagnosis of human African trypanosomiasis has to continue to rely on parasitological evidence and diagnostic tests based on molecular biology should not be used for therapeutic decisions.

49. Treatment protocols for second-stage disease due to *T. b. gambiense* infections have to be adapted in line with the Committee's recommendation to avoid the use of melarsoprol as first-line treatment, and to choose nifurtimox and eflornithine combination therapy as the most suitable treatment.

50. The previously mandatory follow up every six months of all trypanosomiasis patients treated during two years with subsequent lumbar punctures is no longer recommended in view of the efficacy of the first-line medicines currently in use. This change will have an enormous impact on patients' well-being and alleviate the burden on the health system and the workload of health care workers. The current protocols to assess outcome of treatment of trypanosomiasis need to be adapted accordingly.

51. Considering the role that vector control has within an integrated strategy with case detection and therapy for the elimination of trypanosomiasis, vector control tools, methods and strategies must be included in national policies for control and surveillance of human African trypanosomiasis.

52. The Committee recommended strengthening efforts to integrate control and surveillance of human African trypanosomiasis into health systems. The classical vertical approach to combat the disease must be complemented and progressively replaced by the involvement of the health system in control and surveillance, a change that will need increased awareness and capacity building for health workers.

Implications for the Organization's programmes

53. In countries where *T. b. rhodesiense* is endemic, WHO must coordinate with other organizations working on animal health, including other United Nations specialized agencies, in order to control the domestic animal reservoir. In addition, coordination is needed with organizations managing natural

protected areas, as it is in these areas that wild animal reservoirs may be present. This effort implies the participation of Neglected Zoonotic Diseases unit in the Secretariat.

54. During the past years numerous trained staff members experienced in several areas of control and surveillance of human African trypanosomiasis have retired. The Committee identified gaps in human resource capacities in the areas of case detection, patient care, vector control, programme management and operational research. When planning country support, the Organization should include relevant capacity building to ensure that countries are capable of dealing with the disease.

55. A recommendation for clinical product development in human African trypanosomiasis was last made during an informal consultation organized by WHO in September 2004. Following new evidence on treatment outcome assessment presented during the meeting, the Committee identified the need to update the recommendations for clinical product development, suggesting that the Secretariat consider convening a meeting to re-examine the criteria for development of new treatments.

56. The number of cases reported continues to follow a decreasing curve. This trend makes it difficult to enrol cases in clinical trials. Therefore WHO should play a key role in coordinating the activities of national control programmes in charge of control of the disease with those of groups working on development of new tools in order to ensure that the former may access new cases diagnosed and suggest their enrolment in clinical trials.

57. The Committee recognized the leading role of WHO in the elimination process of the gambiense form of human African trypanosomiasis. WHO should continue its work on steering the process of eliminating the disease, in collaboration with Member States and coordinating the work of the different partners and stakeholders.

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