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

Report by the Secretariat

BIOLOGICAL STANDARDIZATION

Fifty-ninth Expert Committee on Biological Standardization Geneva, 13–17 October 2008[2]

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 Expert Committee established 18 new or replacement international reference materials. These are the primary calibrants against which regional or national measurement standards are benchmarked.[3]

3. The Expert Committee also adopted new written standards for **production, control and regulation of snake antivenom immunoglobulins** and an amendment to the current written standard for **yellow fever vaccine**.

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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.964, 2012.

[3] An up-to-date list of WHO International Standards and Reference Materials is available at www.who.int/bloodproducts/catalogue (accessed 23 February 2012).

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. Snake antivenom immunoglobulins (antivenoms) are the only therapeutic products for the treatment of envenomings due to snakebites. The unavailability of effective snake antivenom immunoglobulins to treat the specific types of envenomings encountered in various regions of the world has become a critical health issue at the global level. The crisis has reached its greatest intensity in sub-Saharan Africa, but other regions, such as South-East Asia, are also suffering from a lack of effective and affordable products. The complexity of the production of efficient antivenoms, in particular the importance of preparing appropriate snake venom mixtures for the production of hyperimmune plasma (the source of antivenom immunoglobulins), the decreasing number of producers, and the fragility of the production systems in developing countries further jeopardize the availability of efficient antivenoms in Asia, Africa, the Middle East and South America. Most of the remaining current producers are located in countries where the application of quality and safety standards needs to be improved. The new WHO Guidelines on Production, Control and Regulation of Snake Antivenom Immunoglobulins cover all the steps involved into the production, control and regulation of venoms and antivenoms. The Committee comprehensively covered the current existing experience in the manufacture, control, and preclinical and clinical assessment of these products, and its report aims to serve as a guide to national control authorities and manufacturers to support worldwide production of these essential medicines.

6. The amendment to the written standard for **yellow fever vaccine** requires that the expression of potency of such vaccines be in International Units (IU) per dose. The dose recommended for use in human beings shall not be less than 3.0 $\log_{10}$ IU. This new expression of potency should be approved by national control authorities, and will also be used as the standard for WHO prequalification of yellow fever vaccines. The new way to express the dose of the product is superior from a scientific perspective than the method used previously and will enable products manufactured in different parts of the world to be more easily compared.

Implications for the Organization's programmes

7. The Expert 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.

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

9. The Committee endorsed plans to strengthen the interactions between WHO collaborating centres for biological standardization and national regulatory authorities. One aim is that the centres will assist other countries in their regions and foster the implementation of WHO's written standards and collaboration between laboratories. Establishment of networks of collaborating centres will aid this process.

10. The Chairman of the WHO Blood Regulators Network reported to the Committee on the activities of the network established between six control and regulatory authorities. Its objectives are to address issues 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 are designing a tool that will enable WHO to assess national blood regulatory systems.

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Forty-sixth Expert Committee on Specifications for Pharmaceutical Preparations Geneva, 10–14 October 2011[1]

Main recommendations

11. The Expert Committee on Specifications for Pharmaceutical Preparations 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 from their development phase to their final distribution to the patients. Detailed recommendations can be found under each relevant section in the report.

12. The Forty-sixth Expert Committee adopted 18 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. The Expert Committee members also approved an update of the process for development of monographs for inclusion in *The International Pharmacopoeia*. In addition, one new International Chemical Reference Substance was adopted for use in testing antimalarial medicines.

13. In the area of quality control and regulatory assessment, the Expert Committee responded to an urgent request relating to antimalarial medicines including artemisinin derivatives. The request reflected the public health need expressed by major aid programmes, suppliers, procurement agencies, quality control laboratories and regulators, including the WHO Prequalification of Medicines Programme. The Committee approved new guidance on *Recommendations for quality requirements when artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients,* which responds to urgent requests by major aid programmes with a view to overcoming current shortages in malaria medicines.

14. To support adherence to good manufacturing practices, and in order to keep up-to-date with new trends and standards, a revised good manufacturing practices text was adopted for water for pharmaceutical use.

[1] WHO Technical Report Series, No. 970.

15. In order to support the work of the WHO Prequalification of Medicines Programme, the new *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* was adopted by the Expert Committee with a view to easing the exchange of information by national medicines regulatory authorities.

16. As a first global initiative, the Expert Committee members reviewed and adopted guidance and points to consider for the development for pharmaceuticals entitled *Pharmaceutical development of multisource (generic) pharmaceutical products;* and specifically addressed the *Development of paediatric medicines: points to consider in formulation.*

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

18. The Expert Committee provided new recommendations on the extension of shelf-life in emergencies following the numerous questions raised for oseltamivir and other medicines used during pandemic (H1N1) 2009.

19. The Expert Committee furthermore expressed its support for WHO activities in the area of harmonization of quality assurance and response to new challenges and trends. In this context it fully supported WHO's initiative to organize an international meeting of world pharmacopoeias.

Significance for public health policies

20. The international guidelines, specifications, nomenclature and standards developed under the aegis of the Expert Committee since 1947 are designed to serve all Member States, international organizations, United Nations agencies, regional and interregional harmonization efforts, and underpin important initiatives, including the prequalification of medicines, the Roll Back Malaria Programme, Stop TB, essential medicines and medicines for children.

21. The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities work towards access to good quality medicines. Of particular interest are such authorities as the national medicines regulatory authorities, 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.

22. The activities of the Forty-sixth Expert Committee on Specifications for Pharmaceutical Preparations result in scientifically sound and independent recommendations, written and physical standards, as well as international guidelines for quality medicines. Standards in this area are developed by the Committee following a wide international consensus-building process.

Implications for the Organization's programmes

23. The activities that were discussed during the Forty-sixth Expert Committee have broad intercluster and intracluster relationships and links. There are joint activities, specifically with the WHO Expert Committee on Biological Standardization, and the Expert Committee on the Selection and Use of Essential Medicines as well as its Subcommittee on Medicines for Children. In addition, this Expert Committee develops specific additional guidance and specifications, as needed, for medicines recommended by WHO programmes.

24. The Expert Committee also serves the United Nations Programme on Prequalification of Medicines 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.

25. Based on the Expert Committee's recommendation, WHO is in a position to provide up-to-date standards and guidance in the area of quality assurance of medicines, to the Organization and to relevant external bodies, in response to the need for internationally harmonized approaches in the context of increasing globalization.

26. The recommendations mentioned fully support WHO's objective to support Member States and other relevant bodies involved in supplying medicines, and in providing tools that will help to ensure the safety, efficacy and quality of medicines for maintaining and improving public health.

LEPROSY

Eighth report of the Expert Committee on Leprosy[1] Geneva, 12–19 October 2010

27. The Expert Committee on Leprosy held its eighth meeting in order to analyse the global leprosy situation; to review current developments in areas such as the treatment of leprosy and its various complications; to consider the latest results of research and experience in leprosy control and review existing indicators of progress so as to determine whether better indicators can be introduced; and to advise on the technical and operational matters related to efforts to reduce further the burden due to leprosy.

Main recommendations

28. The Expert Committee recommended a global goal of reducing the rate of occurrence of new cases with visible disability (WHO Grade 2 Disability) to a level below one case per million population at the global rather than the national level. This target is expected to maintain long-term commitment through partnerships with governments, WHO, academia, industry, people affected by leprosy, communities, and nongovernmental organizations.

29. The Expert Committee emphasized the importance of collecting information on the extent of disabilities due to leprosy in terms of total prevalence of Grade 2 disability in the population; the data should cover Grade 2 disability in new cases as well as in people who have completed multidrug therapy. This information is needed for planning rehabilitation services. A milestone would be to reduce by 35% the rate of new cases diagnosed with Grade 2 disability per million population between 2011 and 2015.

30. Relapse after multidrug therapy remains infrequent even after almost three decades of its widespread use, and retreatment with standard multidrug therapy is highly successful. The Expert

[1] WHO Technical Report Series, No. 968, 2012, in press.

Committee recommended surveillance for drug resistance, despite the paucity of reports on drug-resistant strains of *Mycobacterium leprae* after completion of multidrug therapy.

31. Management of disabilities should be part of routine treatment services at the clinic level and also include cured persons. Services available should include provision of aids and appliances, specialist medical care, surgical reconstruction and rehabilitation. Self-care and self-help through counselling of persons in need as well as their family and community members should receive greater emphasis. The strategy of community-based rehabilitation should be applied with local resources to support the rehabilitation of people with disabilities.

32. The Expert Committee stressed the need for research based on new molecular tools in order to improve diagnostics, research into new treatments and subclinical infection, and clinical trials of prevention and treatment of leprosy reactions. It identified some research priorities: developing molecular tools for assessing the emergence of drug resistance; understanding the basis of transmission in order to develop and improve diagnostic tests; finding species-specific antigens that could be used in immunodiagnostic tests; and improving multidrug therapy with better medicines in terms of efficacy and duration of treatment. More research is needed in the area of nerve function impairment and reactions, and on chemoprophylaxis and immunoprophylaxis. Operational, epidemiological and implementation research should be promoted in order to improve the sustainability and quality of leprosy services.

33. The Expert Committee also recommended increased focus on equity, social justice and human rights, stigmatization and gender issues, and a greater contribution from people affected by leprosy in the decision making process.

Significance for public health policies

34. The uneven geographical distribution of leprosy provides an opportunity for countries to focus on areas of relatively high endemicity. The common occurrence of leprosy among contacts of patients also provides an opportunity to detect cases early. The number of new cases detected globally each year has declined steadily over the past 10 years, and at the beginning of 2010, the prevalence of leprosy as reported by countries was about 212 000 cases, corresponding to the number of patients on multidrug therapy at that time. At the same time, all but four countries with a population of more than one million have reached prevalence levels of less than one case per 10 000 population. The strategic approach that had been taken had also resulted in significant improvements in work to prevent and control leprosy, such as simplification of diagnosis and multidrug therapy through provision of blister packs free to all new patients. This progress represented a major public health achievement.

35. Leprosy often causes nerve function impairment as a result of various pathological and immunological processes in the peripheral nerves. The proportion of new cases with such impairment at diagnosis may be as high as 20%. Leprosy reactions are regarded as the leading cause for nerve function impairment, and occur in 30% to 50% of all multibacillary leprosy patients. The mainstay of reaction treatment is corticosteroids. Several studies have demonstrated the usefulness of thalidomide in the treatment of acute erythema nodosum leprosum, but its use is restricted because of its teratogenic effects and ethical and legal considerations. It is important to educate all patients about the signs and symptoms of reactions and nerve function impairment and encourage them to return to health centres as soon as they experience such events. National leprosy programmes should continue to ensure that an efficient referral system exists within the general health services so that nerve function can be assessed in a timely manner and reactions, neuritis and related complications can be diagnosed and dealt with promptly.

36. Disability in new patients and people who have completed treatment remains a challenge. Although prevention and management of disability falls within the broad scope of public health, it requires support from social services, the community and the voluntary sector. Currently, good information is lacking on the extent of disability due to leprosy in terms of the numbers of people affected at global and country levels. It is important to estimate the total prevalence of visible disability (Grade 2 disability) in the population in order to undertake the planning and implementation of rehabilitation services. It will therefore be useful to include in all national programmes a new indicator of the total prevalence of Grade 2 disability in the population. WHO's three-stage disability grading system (0, 1 and 2) has been in use for several years and proven to be a good basis for measuring the magnitude of the problem. Prevention of disabilities begins with early diagnosis of leprosy, recognizing and treating complications such as neuritis and reactions, identifying patients at risk of developing secondary disability, and intervening in time.

37. Progress in further reducing the disease burden may be measured broadly by (i) main indicators requiring minimum amounts of data, (ii) other indicators (some requiring only limited amounts of data and others providing important insights and requiring more detailed information), and (iii) indicators for evaluating the quality of services. The main indicators are: number and rate of new cases detected per 100 000 population per year; number and rate of new cases with Grade 2 disability detected per million population per year; treatment completion and/or cure rate for multibacillary and paucibacillary cases. Use of the Grade 2 disability in newly detected cases as rate per million population will assist in monitoring both case detection and disability (including burden and prevalence).

38. The Expert Committee concluded that most of the recent epidemiological, clinical and pathological studies of coinfection with HIV showed neither an increased prevalence of HIV in patients with leprosy nor an alteration in the clinical spectrum of leprosy among coinfected subjects.

39. The Expert Committee reported that in public health terms it is reasonable to conclude that infectiousness becomes negligible after multidrug therapy is begun.

40. In recent years there has been a change in attitude towards leprosy, with less stigmatization in many countries. People affected by leprosy now more often remain within their families and communities. As a result, involving the family and community members is now seen as a key strategy to empower people affected so as to reduce exclusion and increase inclusion of persons affected by leprosy in different community systems including health, housing, education and decision-making, as well as in socioeconomic settings. Persons affected by leprosy have a major role to play in leprosy services, especially in areas of advocacy, awareness, rehabilitation and case finding. Persons newly diagnosed with leprosy should not be admitted to institutions for long-term care. Timely case-finding and multidrug therapy has prevented disabilities due to leprosy in an estimated two million individuals. There is now a perceptibly higher level of awareness and political commitment in countries where leprosy is endemic, with a renewed emphasis on human rights issues related to stigmatization and discrimination.

41. An important step towards eliminating leprosy would be to focus the approach to prevention and control, taking advantage of the very uneven distribution of the disease within countries and among population groups. Such an approach, which would combine detailed mapping of cases with intensive and innovative efforts towards case detection, is likely to reduce greatly the disease burden. The focused approach should not mean that, in the other geographical areas, population groups will be completely neglected. It is also important to reach persons affected by leprosy living in hard-to-access areas and in underserved and marginalized population groups. In urban populations, which pose special difficulties, the major focus should be on improving the services for people living in the slums.

Contacts of known cases are easily identifiable as individuals at high risk, and may be targeted for specific preventive measures, through either vaccination with BCG or chemoprophylaxis.

Implications for the Organization's programmes

42. The remarkable achievement of reducing the global burden of leprosy over the past quarter century is mainly the result of the application of the recommendations of the WHO Study Group on Chemotherapy of Leprosy on the use of multidrug therapy as the standard treatment, with a combination of three medicines for multibacillary leprosy (rifampicin, clofazimine and dapsone) and two for paucibacillary leprosy (rifampicin and dapsone). Currently, multibacillary patients are treated for 12 months and paucibacillary patients for six months.

43. The current standard multidrug therapy regimens remain the mainstay of leprosy chemotherapy implemented in all countries where leprosy is endemic. The availability of second-line medicines and promising new drugs with high bactericidal activity provide an opportunity to carry out clinical trials of new regimens. Preliminary results of an ongoing trial raise the prospect of reducing the duration of current multidrug therapy to six months for patients with multibacillary leprosy but it is still too early to draw final conclusions.

44. Principles of equity and sustainability are the basis for integration of leprosy within general health services. However, integration does not mean that specialized components should be abolished. The central issue is how to improve the performance of the integrated programme, which should aim at raising community awareness, building capacity, and ensuring regular supervision, technical support, adequate referral, and the availability of multidrug therapy.

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Seventy-fifth Joint FAO/WHO Expert Committee on Food Additives[1] Rome, 8–17 November 2011

Main recommendations

45. The Committee performed risk assessments and made recommendations on the safety of residues of eight veterinary drugs when used for food-producing animals and used in accordance with good veterinary practices. Acceptable daily intake values for these drugs were established and maximum residue limits that are compatible with human health were recommended for specified animal species and tissues.

46. The report also contains general considerations, in particular comments from the risk assessment perspective on documents under elaboration by the Codex Committee on Residues of Veterinary Drugs in Food, which is the risk-management body basing its decisions on the risk assessment advice provided by the Joint FAO/WHO Expert Committee on Food Additives.

47. The Committee also discussed the recommendation of a group of experts to improve the assessment of both acute and chronic dietary exposure to residues of veterinary drugs. This work is

[1] WHO Technical Report Series, No. 969, 2012 (in press).

open for public comment now and will be further discussed by the Committee with a view to strengthening methods for dietary exposure assessment for veterinary drug residues.

48. The assessments, recommendations and comments provided by the Committee will be discussed by the Codex Committee on Residues of Veterinary Drugs in Foods at its twentieth session in May 2012 in order to identify and recommend risk-management measures and appropriate risk-mitigation measures to reduce human exposure, where necessary.

49. WHO has published summaries of the toxicological and other related information upon which the safety assessments of the compounds were made,[1] and FAO has published summaries of the identity and purity of food additives.[2]

Significance for public health policies

50. The Committee's work identifies, and if possible quantifies, the public health significance of exposure to chemicals in food, in this case residues of veterinary drugs, 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 (i.e. the Codex Alimentarius Commission and its subsidiary bodies).

51. 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 residues of veterinary drugs in food 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.

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

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

Implications for the Organization's programmes

54. 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 had originally been planned to be held in 2010–2011; two were held in 2010 on food additives and contaminants and one in June 2011 on food additives and contaminants. The 75th meeting, the fourth of the biennium, was organized in response to urgent requests from Member States through the Codex Alimentarius Commission and with specified funds provided through FAO.

[1] WHO Food Additives Series No. 66, 2012.

[2] Food and Agriculture Organization of the United Nations. *Compendium of food additive specifications*. Joint FAO/WHO Expert Committee on Food Additives, 75th meeting, 2011. JECFA Monographs 12, FAO, 2012 (in press).

55. WHO is a partner in the Joint FAO/WHO Food Standards Programme, whose principal organ is the Codex Alimentarius Commission. The Committee's work is crucial to the work of the Commission. International standards and recommendations on residues of veterinary drugs in food, on food additives and contaminants in food developed by the Codex Alimentarius Commission are based on the work of the Joint FAO/WHO Expert Committee on Food Additives.

56. WHO Representatives and staff in regional offices also make use of the Committee's evaluations when advising Member States on food safety issues.

ACTION BY THE EXECUTIVE BOARD

57. The Board is invited to note the report.

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