World Health Organization

EXECUTIVE BOARD
130th session
Provisional agenda item 10.1

EB130/34
15 December 2011

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

Report by the Director-General

THE SELECTION AND USE OF ESSENTIAL MEDICINES

Report of the WHO Expert Committee, 2011 (including the WHO Model List of Essential Medicines: 17th list and the WHO Model List of Essential Medicines for Children: 3rd list)
Accra, 21–25 March 2011[2]

1. The 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Accra, Ghana, on 21–25 March 2011, the first meeting of the Committee to be held outside Geneva. The purpose of the meeting was to update the 16th WHO Model List of Essential Medicines and the second WHO Model List of Essential Medicines for Children.

Main recommendations

2. The Committee reviewed the evidence and added the artesunate plus amodiaquine combination tablet for the treatment of malaria in adults and children, in line with current WHO treatment guidelines. In making its decision, the Committee reviewed the latest clinical evidence and the information about licensing in several countries of the fixed-dose combination tablet. The Committee noted, however, that appropriate doses of both medicines can also be achieved using combinations of the single-component products, including co-blistered presentations.

3. The Committee added a tranexamic acid injection for the treatment of adult patients with trauma and significant risk of ongoing haemorrhage to the 17th List on the basis of the results of a large trial of the use of tranexamic acid specifically for trauma patients – including those with road traffic injuries. The Committee concluded that there is sufficient evidence to support the proposal that listing tranexamic acid may contribute to a reduction in this cause of death.

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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 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. 965, 2011.

4. A glucagon injection (of 1 mg/ml) was indicated for the treatment of acute severe hypoglycaemia in patients with diabetes – to support efforts in many countries to ensure that the appropriate treatment was added to the Lists, in view of the increasing number of patients with diabetes. The Committee also recommended that careful attention be paid to the cost of procuring glucagon and noted that based on the experience with other high-cost medicines, such as the antiretrovirals, inclusion in the Lists of Essential Medicines may help reduce prices.

5. The Committee added misoprostol tablet (200 µg) for the prevention of postpartum haemorrhage, where oxytocin is not available or cannot be safely used. WHO guidelines currently recommend that misoprostol can be used to prevent and treat postpartum haemorrhage due to uterine atony "in situations where there is no other treatment available". New evidence submitted to the Committee showed that misoprostol can be safely administered to women to *prevent* postpartum haemorrhage by traditional birth attendants or assistants trained to use the product at home deliveries. The Committee stressed that misoprostol should *not*, however, be used *to treat* haemorrhage unless there is no other option available. The Committee observed that, if it is available, oxytocin is recommended as it is more effective and cheaper.

6. Other medicines that were added to the 17th Model List were: clarithromycin, paclitaxel and docetaxel, bisoprolol, and atracurium; and to both Lists were: isoflurane, propofol, miltefosine, midazolam, terbafine cream/ointment, and mupirocin cream/ointment.

7. The Committee reviewed the available evidence on analogue insulins compared to recombinant human insulin and concluded that analogue insulins currently offer no significant clinical advantage over recombinant human insulin and there is still concern about possible long-term adverse effects.

8. The Committee reviewed the report of a supplementary meeting of the Expert Committee that took place in Geneva on 15 January 2010 to consider whether oseltamivir and zanamivir should be added to the 16th List of Essential Medicines in the context of the pandemic of influenza A (H1N1) 2009 virus infection. Applications for the inclusion of these medicines had previously been considered in 2009, and both had been rejected. The Committee ratified the report of the between-sessions meeting and decided to retain oseltamivir on the Lists of Essential Medicines, to be used according to WHO treatment guidelines. The Committee also noted the usefulness of the between-sessions meeting and recommended that such arrangements be put in place in the future, as needed.

Significance for public health policies

9. With the addition of artesunate plus amodiaquine to both Lists, countries endemic for malaria will have a wider choice of treatments.

10. The inclusion of tranexamic acid in the 17th List will contribute to its wider use, a decrease in the number of deaths due to trauma-induced haemorrhage and an eventual reduction in its price.

11. The Committee considered that the analogue insulins currently offer no clinical advantages over recombinant human insulin and that there is concern about the possible long-term adverse effects. The guidance provided by the Committee will assist national programmes in achieving value for money in their procurement activities.

Implications for the Organization's programmes

12. The continued updating of the Model Lists provides WHO, United Nations programmes and Member States with a critical tool in the procurement of medicines and related supplies.

13. The processes involving the Lists of Essential Medicines, including the supplementary sessions (between-meeting sessions), offer WHO an excellent rapid advice mechanism on the selection and use of medicines.

14. The review and use of evidence as well as the transparent manner in which the Committee runs, offer a model for use in countries on achieving optimal selection and use of medicines.

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS IN FOOD

Seventy-fourth Joint FAO/WHO Expert Committee on Food Additives Rome, 14–23 June 2011[1]

Main recommendations

15. The Committee made recommendations on the safety of 12 food additives or groups of additives. Acceptable daily intakes were provided and advice on other safety issues was given. In particular, the safety of aluminium-containing food additives was re-evaluated in the light of total exposure to aluminium and potential health implications. The Committee concluded that estimated dietary intake for adults and children is at or above the health-based guidance value (tolerable intake) and therefore recommended that provisions for the maximum use level of aluminium-containing food additives in the Codex General Standard for Food Additives be reviewed.

16. The Committee also made recommendations on the health risks of two important groups of contaminants: the natural toxins cyanogenic glycosides and the mycotoxins fumonisins. Cyanogenic glycosides occur in a number of plants, for example, cassava. When these plants are consumed, cyanide can be formed, which has led to acute poisoning as well as various diseases, such as konzo (spastic paraparesis) or tropical ataxic neuropathy. The Committee established an acute and a chronic tolerable intake level for cyanogenic glycosides on the basis of the cyanide content, from which new limits for cyanide and cyanide precursers in food can be derived. Regarding fumonisins, with maize being the main source of exposure, the Committee established a revised tolerable-intake level and concluded that exposure in several parts of the world exceeds this safe exposure level. It recommended implementation of maximum limits of fumonisins in maize, as proposed by the Codex Committee on Contaminants in Food.

17. The report also contains general considerations, in particular on adequate and timely data submissions to allow for complete evaluation, as well as a number of recommendations for further research.

[1] WHO Technical Report Series, No. 966, 2011.

18. These assessments will be discussed at upcoming meetings of the Codex Committee on Food Additives and the Codex Committee on Contaminants in Food to identify and recommend appropriate risk mitigation and management measures to reduce human exposure where necessary.

19. WHO is publishing summaries of the toxicological and related information upon which the safety assessments of the compounds were made.[1] FAO is publishing summaries of the identity and purity of food additives.[2]

Significance for public health policies

20. 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 FAO/WHO Food Standards Programme (i.e. Codex Alimentarius Commission and its subsidiary bodies).

21. 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 on contaminants and 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.

22. The Committee's recommendations are used by the Codex Alimentarius Commission for setting international food 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.

23. 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

24. 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 2010–2011, two were held in 2010 on food additives and contaminants, and one was held in June 2011 on food additives and contaminants. A fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives was held in November 2011 to evaluate residues of veterinary drugs in food, with funds provided through FAO.

25. WHO is a partner in the Joint FAO/WHO Food Standards Programme, which administers the Codex Alimentarius Commission. The Committee's work is crucial for the work of the Codex Alimentarius Commission. International standards and recommendations on food additives and

[1] Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 65 (in preparation).

[2] Food and Agriculture Organization of the United Nations. *Compendium of food additive specifications.* Joint FAO/WHO Expert Committee on Food Additives, 74th meeting. FAO JECFA Monograph 11, Rome, FAO (in press).

contaminants in food developed by the Codex Alimentarius Commission are based on the work of the Joint FAO/WHO Expert Committee on Food Additives.

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

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Fifty-seventh meeting of the Expert Committee
Geneva, 23–27 October 2006
Fifty-eighth meeting of the Expert Committee
Geneva, 8–12 October 2007

Main recommendations

27. 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 ensuring the quality, safety and efficacy of such substances and to the establishment of international reference materials.

28. 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 the comparison of data worldwide. Based on the results of international collaborative laboratory studies, the 57th meeting of the Expert Committee established 15 new or replacement international reference materials;[1] similarly, the 58th meeting established 13 such materials.[2] These are the primary calibrants against which regional or national measurement standards are benchmarked. An up-to-date catalogue of international reference materials is available.[3]

29. The 57th meeting of the Expert Committee[4] proposed new written standards for human papillomavirus vaccines, meningococcal A conjugate vaccine, and a new standard that defines regulatory expectations for the evaluation of the thermal stability of vaccines. The Committee also endorsed the strategic initiative proposed by WHO in the areas of quality, safety and efficacy of blood products, and quality of related in vitro diagnostic devices during the next five to seven years. The 58th meeting of the Committee[5] proposed new written standards for inactivated Japanese encephalitis vaccine for human use; on regulatory preparedness for pandemic influenza vaccines; and for clinical evaluation of meningococcal C vaccines.

[1] See WHO Technical Report Series, No. 962, Annex 4, in press.

[2] See WHO Technical Report Series, No. 963, Annex 4, in press.

[3] See http://www.who.int/bloodproducts/catalogue/en/index.html (accessed 22 November 2011).

[4] WHO Technical Report Series, No. 962, in press.

[5] WHO Technical Report Series, No. 963, in press.

Significance for public health policies

30. 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' reference preparations, and often form the basis for licensing, routine lot release and clinical dosing worldwide.

31. Human papillomavirus vaccines have considerable potential to prevent morbidity and mortality due to certain types of cervical cancer. The new WHO written standard paved the way for prequalification of the vaccines and hence, will improve access to the vaccine in countries where cervical cancer imposes a high disease burden.

32. The new written standard for meningococcal A conjugate vaccine also facilitated the prequalification of this vaccine. Although group A isolates were at one time a common cause of meningococcal disease worldwide, they are now principally responsible for recurrent epidemics in the "meningitis belt" countries in sub-Saharan Africa. A major epidemic is anticipated in the near future, and the availability of this WHO guidance will assist Member States in the evaluation and licensure of candidate vaccines.

33. A global network of key regulatory authorities engaged in and responsible for pandemic influenza vaccine regulation developed the WHO guidelines on regulatory preparedness for pandemic influenza vaccines. The guidelines are intended to provide state-of-the-art advice and recommendations to national regulatory authorities concerning: regulatory pathways for human pandemic influenza vaccines; regulatory considerations to be taken into account in evaluating the quality, safety and efficacy of candidate vaccines; and recommendations for effective post-marketing surveillance of these vaccines. These guidelines provide policy-makers with guidance on business continuity plans for regulatory agencies as well as regulatory preparedness.

34. Japanese encephalitis is the most important viral encephalitis affecting countries of south-east Asia and the western Pacific. Transmission has intensified in certain countries over the past 25 years, and the disease has also extended its geographical range to previously unaffected areas of Asia and to northern Australia. The Expert Committee had previously recommended that WHO guidance for inactivated Japanese encephalitis vaccines be revised in the light of new information on vaccine production and quality control, and that sections on nonclinical and clinical evaluation be included in the amended text. Accordingly, a revised text was considered and adopted by the Committee, which also encouraged the development of cell-culture-derived vaccines in preference to mouse-brain-derived vaccines.

Implications for the Organization's programmes

35. The Expert Committee on Biological Standardization 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 responsibilities in this area.

36. The observations, conclusions and recommendations of the Expert Committee have significant implications for several of WHO's activities. In particular, the Committee provides timely recommendations and reference preparations for ensuring 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 international parties, such as UNICEF and PAHO.

37. New written guidance that defines regulatory expectations for the evaluation of the thermal stability of vaccines is a groundbreaking standard that opens a new regulatory pathway for vaccine stability studies. To promote and gain experience in the evaluation of vaccine stability, a series of in-country workshops has been conducted to translate the standard into regulatory practice.

38. The endorsement of the strategic initiatives that WHO aims to undertake in the areas of quality, safety and efficacy of blood products and quality of related in vitro diagnostic devices provides strategic direction for the blood products and related programme. In addition, the goal to develop a strategic plan to strengthen the establishment of WHO global measurement standards with emphasis on blood safety was also endorsed.[1]

39. WHO publishes authoritative information on the assignment of infectivity for transmissible spongiform encephalopathies in human and animal tissues, which may be used in the manufacture of medicinal products. This information is intended to assist national regulatory authorities and manufacturers in conducting risk assessment studies and selecting measures to reduce the risk of transmitting, through medicinal products, transmissible spongiform encephalopathies. Any attempt to construct an assessment of risk from biological and other pharmaceutical products should begin with an evaluation of infectivity in the human or animal tissues from which these products are derived. The Expert Committee updates WHO guidance, based on advice from an expert advisory group, and establishes the standard for the prequalification of vaccines and medicines.

40. The Committee endorsed plans to strengthen 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 written standards and interlaboratory collaborations. Establishment of networks of collaborating centres will be an aid to this process.

41. The WHO Blood Regulators Network reported to the Committee the activities of the network established among six control and regulatory authorities. The Network's objectives are to address relevant issues, share expertise and information, move towards a convergent regulatory policy and seek solutions to emerging public health challenges. The Network members are developing a tool to enable WHO to assess national blood regulatory systems.

TOBACCO PRODUCT REGULATION

Report of the sixth meeting of the WHO Study Group on Tobacco Product Regulation Buenos Aires, 22–24 November 2010[2]

42. The WHO Study Group on Tobacco Product Regulation has launched a series of reports to provide a scientific foundation for tobacco product regulation. In line with Articles 9 and 10 of the

[1] WHO Technical Report Series, No. 963, in press.

[2] WHO Technical Report Series, No. 967, 2011.

WHO Framework Convention on Tobacco Control, these reports identify approaches for the regulation of tobacco products. Such products pose significant public health issues and raise questions on tobacco control policy.

43. The report of the sixth meeting deals with two important issues related to tobacco product regulation: the dependence potential of tobacco products; and health risks from exposure to toxic metals in smokeless tobacco products and from cigarette smoke. Of the topics discussed at the sixth meeting of the Study Group, these issues were deemed by the experts to be the most critical for the issuance of recommendations for regulation.

Toxic elements in tobacco and in cigarette smoke

Main recommendations

44. Toxic metals and metalloids constitute one of the more understudied major carcinogenic chemical classes in smokeless tobacco products and tobacco smoke. The analysis of toxic metals in tobacco is relevant to health concerns. This report summarizes available evidence related to the health risks from exposure to toxic metals in smokeless tobacco products and from cigarette smoke. Given the number of metals or metalloids found in tobacco, owing in part to the incorporation into the tobacco plant of the metallic elements in soil where tobacco is grown, this report is limited to a discussion of toxic or carcinogenic metals reported at significant concentrations. Thus, though there are other toxic metals in tobacco that warrant investigation, the metals outlined and described in this report are considered of greatest concern due to concentration in tobacco or smoke, carcinogenicity and other toxic effects. In this regard, a number of research recommendations are presented in the report.

Significance for public health policies

45. The extent to which consumption of a particular tobacco product confers additional toxic metal exposure risks is an important question. Smokeless tobacco products are consumed in a much different manner from cigarette tobacco or other tobacco products that are for smoking. Whether the product is consumed in a smokeless form or by smoking influences overall exposure and subsequent associated health risks directly to the tobacco consumer and possibly to people in close proximity who are subjected to exposure in the form of second-hand smoke. For example, biochemically and pathologically, there is strong evidence for airway sensitization and inflammation, including atopic inflammation, as a consequence of exposure to tobacco smoke particulate. Studies have also demonstrated that metals present in the particulate matter are responsible for inducing production and release of inflammatory mediators by the respiratory tract. Similarly, it is evident from dental studies that oral exposure to individual metals may have an impact on health.

Implications for the Organization’s programmes

46. There are five major classes of carcinogens in tobacco smoke, of which some have been carefully studied, contributing to a strong weight of evidence for associated health risks. Toxic metal exposure from smokeless tobacco products and associated health risks have been studied to a very limited degree compared to particulate metal inhalation toxicology. It is recognized that toxic metals and metalloids constitute one of the more understudied major carcinogenic chemical classes in smokeless tobacco products and tobacco smoke. Thus, in order to provide better policy guidance to Member States in relation to smokeless tobacco products, the report stresses the need for further studies on metal concentrations in smokeless tobacco, smokeless tobacco additives, and cigarette

tobacco produced over all geographical areas. In addition, research should be conducted to determine the factors, including soil levels and environmental conditions, which lead to higher tobacco product constituent levels of metals. Recommendations should be developed which restrict the growing of tobacco in regions with high soil metal content. Given that the extent to which consumption of a particular tobacco product confers additional toxic metal exposure risks is an important public health question, WHO should recommend a broader research agenda focusing on the study of metals or metalloids that are, according to the classifications of the International Agency for Research on Cancer, group 1 human carcinogens, group 2a probable human carcinogens, or group 2b possible human carcinogens.

Discussion of the basis for a regulatory framework to reduce the dependence potential of tobacco products

Main recommendations

47. The foundation for a regulatory framework to reduce tobacco-product dependence potential is the scientific understanding of the determinants of tobacco dependence and evidence that the design and manufacturing of tobacco products can increase or decrease dependence potential. The primary dependence-producing drug in tobacco is nicotine. Tobacco products are designed to optimize the addictive effects of nicotine, while nicotine replacement therapy products are designed to minimize them. Several decades of research have shown that the dependence-producing effects of nicotine are directly influenced by the dose and speed of nicotine absorption, by other ingredients and design features, and by associated sensory and environmental stimuli. Tobacco companies understood this much earlier. They used this knowledge to optimize dosing characteristics and employed ingredients and designs to optimize dependence potential. Designs and ingredients were also intended to increase product attractiveness and ease of initiation to youth, women and other target populations. This recommendation has been developed because tobacco companies have not been restricted in their ability to design and manufacture products to increase dependence potential and attractiveness; the intent of the companies is to increase tobacco product use and dependence by undermining prevention and cessation tobacco control measures. This recommendation provides specific conclusions and recommendations for regulatory policy addressing a framework for reducing the dependence potential of tobacco products.

Significance for public health policies

48. Experiences with pharmaceutical nicotine delivery systems and other drug delivery systems have demonstrated that dependence potential can be altered by the design of the product. For drug products, including smoking cessation medications, minimizing dependence potential is an explicit goal of manufacturers and regulators. Although tobacco products are exempt from such international and national drug regulatory controls and frameworks, such regulatory approaches demonstrate that dependence potential and attractiveness can be regulated. The principles and experience applied to such drug regulation could be applied to tobacco product regulation in order to ensure that tobacco products are no longer designed and manufactured to optimize dependence potential and attractiveness. The WHO Study Group on Tobacco Product Regulation maintains that a regulatory framework designed to reduce the dependence potential and attractiveness of tobacco products could improve public health by contributing to more effective tobacco control efforts to reduce initiation, the prevalence of tobacco use and resulting disease and death.

Implications for the Organization's programmes

49. In the light of strategies employed by the tobacco industry to manipulate the nicotine-dosing capacity of its products and, consequently, increase tobacco-product dependence potential, WHO should promote approaches for regulation that could be used to reduce dependence potential under a regulatory framework. In so far as the main addictive substance in tobacco is nicotine, WHO should provide guidance to Member States concerning the scientific foundation and potential approaches for a regulatory framework for reducing the dependence potential of tobacco products. This should be undertaken with the aim of reducing the prevalence of tobacco use and harm by reducing the risk and severity of dependence as a biological force that contributes to the perpetuation of tobacco use. As tobacco products pose certain challenges that are more complex and may be more difficult to address than those posed by regulated drug products, WHO should support the need for a better understanding of the dose–response relationship between nicotine administration and dependence, and how various pharmacological and non-pharmacological factors alter dependence potential and the risk of dependence.

ACTION BY THE EXECUTIVE BOARD

50. The Board is invited to note this report.

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