



# WORLD HEALTH ORGANIZATION

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## **Expert committees and study groups<sup>1</sup>**

### **Report by the Secretariat**

#### **WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION**

**Fifty-third report<sup>2</sup>**  
**Geneva, 17-21 February 2003**

#### **Main recommendations**

1. The Expert Committee on Biological Standardization reviews developments in the field of biological substances used in human medicine, which include vaccines, plasma products and biological therapeutics. It coordinates activities leading to the adoption of recommendations for assuring their quality, safety and efficacy and to 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. Based on the results of international collaborative laboratory studies, the Expert Committee established 16 new or replacement international reference materials. Additionally, one international reference material no longer required was discontinued. An up-to-date list of WHO international standards and reference materials is available on the WHO web site.
3. The Committee adopted new guidelines on regulatory expectations for the elimination, reduction or replacement of thiomersal in vaccines; a revision of recommendations for production and quality control of smallpox vaccine; new guidelines on the safe production and quality control of inactivated poliovirus vaccines manufactured from wild-type polioviruses; and an addendum to the recommendations for the production and quality control of group C meningococcal conjugate vaccines relating to the use of serological surrogates of protection.
4. The Committee agreed that the report of a WHO consultation held in Geneva in February 2003 on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products

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<sup>1</sup> 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.

<sup>2</sup> WHO Technical Report Series, No. 926, 2004, in press.

should be published as soon as possible and be presented at the Committee's next meeting so that the report's wider implications for biological standardization could be considered.

5. It was considered timely to review the requirements for the collection, processing and quality control of blood, blood components and plasma derivatives which were last revised in 1992. The Committee emphasized the importance of WHO continuing to provide recommendations in this area.

### **Significance for public health policies**

6. Recommendations published by WHO provide guidance for national regulatory authorities and manufacturers on production, quality control and associated safety and regulatory issues. These serve as the basis for national regulations. WHO's 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.

7. Making changes to the thiomersal content of vaccines already licensed with this preservative is a complex issue that requires careful consideration. Experience shows that eliminating thiomersal from an existing product or reducing its content may have some unexpected effects on vaccine quality, safety or efficacy, including changes in stability. In the new guidelines, the general principles of evaluating a vaccine after the elimination, reduction in content, removal or replacement of thiomersal from an already-licensed vaccine are discussed, with particular attention being given to the regulatory expectations for each of the above possibilities.

8. The recommendations (formerly requirements) for production and control of smallpox vaccine were last revised in 1965. After the disease had been declared eradicated in 1980, the Global Commission for the certification of Smallpox Eradication recommended that a global stockpile of vaccine should be established, in parallel with national stockpiles. However, a survey conducted by WHO in 2001 found that only small amounts of stockpiled smallpox vaccine exist. These stocks are distributed unevenly around the world and accessible to only a selected part of the global population. Additional production would be needed to meet any major demand on vaccine supply, such as that which might follow an intentional release of smallpox virus. Resumption of smallpox vaccine production would benefit from modern concepts of production and control, and modern regulatory expectations should be adhered to in the licensing process. The revised recommendations provide state-of-the-art guidance for new vaccine manufacture and testing for each type of substrate used for vaccine production.

### **Implications for the Organization's programmes**

9. The Expert Committee's work enables WHO to fulfil its constitutional responsibilities. In particular, its observations, conclusions and recommendations 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 plasma products. The global norms and standards defined by the Committee provide the basis for assessing the acceptability of vaccines for purchase by international agencies.

10. In the context of a world on the threshold of the eradication of poliomyelitis, there is a need for effective containment of wild-type poliovirus strains as a precondition of global certification of eradication of the disease. The new guidelines on the safe manufacture of inactivated poliovirus vaccines from wild-type polioviruses and their quality control specify steps to minimize the risk of reintroducing wild-type poliovirus from a vaccine-manufacturing facility into the community.

## WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

### **Fifty-fourth report<sup>1</sup>**

**Geneva, 17-21 November 2003**

#### **Main recommendations**

11. The Committee, drawing on the results of international collaborative laboratory studies, recommended the establishment of 14 new or replacement international reference materials. The Committee also adopted new recommendations for the production and quality control of pneumococcal conjugate vaccines, revised recommendations for production and quality control of influenza vaccines, new guidelines for the nonclinical evaluation of vaccines, and the amendments to the recommendations on reference materials and for potency assays of diphtheria, tetanus and pertussis vaccines.

12. The Committee also considered a report that, in the period November 2002 to February 2003, several cases of poliomyelitis were observed in one country after vaccination with the oral poliomyelitis vaccine and that the MEF-1 reference wild-type poliovirus type 2 strain was isolated in each case. Studies demonstrated the presence of the MEF-1 strain in vials of one vaccine batch. The Committee was asked to consider the wider implications of this episode and concluded that prevention of deliberate interference with a product requires safeguards that differ from those in normal good manufacturing practice. Measures to ensure that vials are tamper-proof and procedures to detect counterfeiting are required. In this context WHO was advised to obtain additional specialist advice, and to make this available to all vaccine manufacturers, distributors and national regulatory authorities.

#### **Significance for public health policies**

13. The general significance of WHO's guidance has been noted above (see paragraph 6). Since the last revision of WHO's requirements for production and quality control of influenza vaccines, there have been significant developments. Subunit and split vaccines are now widely used and the effective dose of haemagglutinin has been established. In addition vaccines containing adjuvants have been developed and approved. The danger of pandemics due to the appearance of novel and highly pathogenic strains of influenza virus presents several challenges for production and administration of suitable vaccines. The new recommendations facilitate the production of vaccines against pandemic strains by establishing specifications for the use of cell cultures and also of reverse genetic techniques to derive suitable prototype strains for vaccine production.

14. The range of novel vaccines under development is broad. There is a need for guidance, based on best scientific knowledge, on the type and extent of nonclinical evaluation of such products, as that forms an essential part of the quality assessment of a vaccine candidate. The new guidelines are intended to set out principles for nonclinical evaluation of vaccines and to provide information and guidance to vaccine manufacturers and recommendations for national regulatory authorities on such evaluation and quality assessment. The report outlines regulatory expectations and is intended to complement, and should be read in conjunction with, the WHO Guidelines for clinical evaluation of vaccines: regulatory expectations.

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<sup>1</sup> WHO Technical Report Series, No.927, 2005, in press.

## **Implications for the Organization's programmes**

15. The preceding report outlines the general implications. The current First International Standard for Hepatitis B Surface Antigen needs replacement. A collaborative study had been performed to assess the suitability of a candidate replacement preparation and to calibrate it in International Units. The results and related biochemical data indicated no drift in the value of the International Unit over 18 years. In contrast, one Member State and one manufacturer had assigned values in nanograms of protein to secondary standards. The study showed that it was not appropriate to assign SI unit values to biological reference materials, thus vindicating the approach to biological standardization espoused by WHO.

16. The Committee was informed of the growing numbers globally of transplants of organs, tissues and cells. Limitations of supply determine the number of transplant operations and prevent demand being met. Globally there is a wide variety of tissue banks and transplant materials cross boundaries in all WHO regions. Complex processes may be needed for handling tissues and cells for transplantation. The use of human tissue, the risk of transmission of pathogens and misuse of resources all raise ethical and public health concerns. Although this area represents a new sphere of activity, the Committee agreed that it has a role to play and invited submission of detailed and prioritized proposals relating to safety and efficacy, good manufacturing practice and quality management systems, consistent with WHO recommendations for other therapeutic materials.

## **EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS**

### **Sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives<sup>1</sup> Rome, 10–19 June 2003**

#### **Main recommendations**

17. The Committee made recommendations on the safety of several food additives, contaminants, and flavouring agents, and evaluated a water-treatment agent and a nutritional source for iron. It prepared or reviewed specifications for many food additives and flavouring agents. Its report contains some general recommendations on, for example, on the principles of safety assessment of flavouring agents and the principles for intake assessment for food additives.

18. The Committee evaluated a total of 24 food additives, seven of them for specifications only. All the others underwent toxicological evaluation as well, and acceptable daily intakes were established. Limits for heavy metals were revised for 39 food additives, and a total of 144 flavours belonging to seven different chemical classes were evaluated by application of the decision-tree procedure previously established by the Committee. In addition 101 flavouring agents were considered for specifications only. Evaluation of new data on two contaminants (cadmium and methylmercury) allowed tolerable daily intake values to be determined. A tolerable daily intake was also established for a water-treatment agent, sodium dichloroisocyanurate. Ferrous glycinate processed with citric acid was evaluated as a nutritional source of iron and considered suitable for this purpose, provided that the total intake of iron did not exceed the provisional maximum tolerable daily intake. Summaries of the toxicological and related information on which the safety assessments of the compounds were made

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<sup>1</sup> WHO Technical Report Series, No. 922, 2004.

and of the identity and purity of food additives and flavouring agents will be published by WHO and FAO, respectively.

### **Significance for public health policies**

19. The Committee's work emphasizes the public health significance of the risk assessment of additives, flavouring agents, and chemical and veterinary drug residues in food. It highlights the complexity of the process, which includes assembling and analysing all relevant data; interpreting studies of, for instance, carcinogenicity, genotoxicity, reproductive toxicity and teratogenicity; extrapolating to human beings the effects observed in experimental animals; and characterizing hazards to human beings, based on available toxicological and epidemiological data.

20. Although all Member States face the problem of assessing potential risks of chemicals in food, only a few national or regional scientific institutions can assess the relevant toxicological and related data. Member States therefore need to be provided with valid information on both the general aspects of risk assessment and the specific evaluations on additives, flavouring agents and contaminants covered in this report. The Committee's complex work in reaching an international consensus on the evaluation of these compounds means that no other body has comparable influence on public health decisions related to food safety.

21. The Committee's recommendations are used by the Codex Alimentarius Commission for setting international food safety standards. Such values are established only for substances that have been evaluated by the Committee and have been allocated an acceptable daily intake or a tolerable daily intake, so ensuring that food commodities in international trade meet strict safety standards.

### **Implications for the Organization's programmes**

22. The evaluation by the Committee of chemicals in food is a continuing activity. Four meetings (two on food additives, one on contaminants, and one on residues of veterinary drugs in food) are scheduled for 2004-2005.

23. WHO is a partner in the Joint FAO/WHO Food Standards Programme, which administers the Codex Alimentarius Commission. The Committee's work is crucial to that of the Commission.

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

## **EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD**

### **Sixty-second report of the Joint FAO/WHO Expert Committee on Food Additives<sup>1</sup> Rome, 4-12 February 2004**

#### **Main recommendations**

25. The Committee made recommendations on the safety of veterinary drug residues in food. Residues for monitoring purposes were defined where appropriate and maximum residue limits were recommended when the drugs are administered to food-producing animals in accordance with good practice in the use of veterinary drugs. The report contains also a number of general recommendations of relevance to the work of the Committee.

26. The Committee also recommended acceptable daily intake levels for 10 veterinary drugs, including three antimicrobial agents (cefuroxime, flumequine and pirlimycin), two insecticides (cyhalothrin, and cypermethrin/ $\alpha$ -cypermethrin) and one feed additive (ractopamine). The Committee evaluated the safety of low concentrations of the antimicrobial agent chloramphenicol in animal products, and commented on the possible sources for low levels of chloramphenicol in food. It concluded that there was no evidence to support the hypothesis that chloramphenicol is synthesized naturally in detectable amounts in soil. Also, there was evidence that the low concentrations of chloramphenicol detected by food-monitoring programmes in 2002 could not originate from residues of chloramphenicol persisting in the environment after historical veterinary use of the drug in food-producing animals. Because of the high variability in the half-life of chloramphenicol in different environmental conditions, however, such a mechanism might occasionally cause low-level contamination in food. Summaries of toxicological and related information on which the safety assessments of the compounds were made and of the identity and purity of food additives and flavours will be published by WHO and FAO, respectively.

#### **Significance for public health policies and implications for the Organization's programmes**

27. These are summarized in the preceding report.

## **TOBACCO PRODUCT REGULATION**

### **Report of a WHO Study Group Montebello, Canada, 25-28 October 2004**

28. Tobacco products are uniquely hazardous to human health but are largely unregulated throughout the world. There is an urgent need to provide the best available science and technology to guide the implementation of Articles 9, 10 and 11 of the WHO Framework Convention on Tobacco Control, which concern tobacco-product regulation. Major limitations and tasks include the following:

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<sup>1</sup> WHO Technical Report Series, No. 925, 2004, in press.

- Tar, nicotine and carbon monoxide yields in cigarette smoke measured using the machine testing protocol of the International Organization for Standardization are misleading.
- Meaningful standards are needed for testing of other tobacco products.
- Guidelines for evaluating new tobacco products with harm reduction claims must be prepared to enable their potential risks and benefits to be assessed by WHO and other health organizations.
- Research and testing capacity needs to be established and sustained in order to regulate existing and future tobacco products.

29. In November 2003 the Scientific Advisory Committee on Tobacco Product Regulation was formalized as the WHO Study Group on Tobacco Product Regulation in order to provide such guidance. The Study Group advises the Organization by generating evidence-based recommendations for Member States to create a coordinated regulatory framework for tobacco products. The Study Group comprises scientific experts on product regulation, treatment of tobacco dependence, product design and manufacture, and laboratory analysis of tobacco ingredients and emissions.

### **Main recommendation**

30. The Study Group adopted the recommendation on the Guiding principles for the development of tobacco product research and testing capacity and proposed protocols for the initiation of tobacco product testing at its first meeting. The recommendation is based on discussions and papers presented at the Sixth meeting of the WHO Scientific Advisory Committee on Tobacco Product Regulation (Goa, India, 25-27 September 2003).<sup>1</sup>

31. The primary goal of establishing and coordinating worldwide the physical and human resources for research and testing is to provide a scientific basis for improving public health through tobacco-product regulation. Laboratory capabilities for both research and testing must be developed. The consequent emergence of laboratory capacity must be internationally facilitated and coordinated in order to implement the Framework Convention. Transparency in operations is necessary to provide regulatory authorities and the public with confidence in the integrity of laboratory operations and findings. Existing independent laboratories serving the tobacco industry provide potential laboratory capacity, but, if they are to be used to serve public health regulation, provisions must be put into place to assure independence of operations and credibility. Appropriate “firewalls” must be built into contracts drawn up with such laboratories.

32. Surveillance of health effects and knowledge about patterns of use are crucial in order to determine responses, both desired and unintended. The inadequacies of the International Organization for Standardization’s protocol demonstrate the need for testing procedures that reflect public health concerns in evaluating novel and existing tobacco products. Research, surveillance and testing capacity must anticipate and respond to rapid evolution of products. This recommendation proposes that all new tobacco products and modified existing products should be subject to pre-market review by regulatory authorities. Rigorous pre-market review is especially important when “harm reduction” claims are made or expected.

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<sup>1</sup> TobReg Recommendation: Guiding principles for the development of tobacco-product research and testing capacity and proposed protocols for the initiation of tobacco product testing. Geneva, World Health Organization, 2004.

### **Significance for public health policies**

33. It is expected that the entry into force of the Framework Convention and implementation of its provisions will lead to a rapid expansion of regulatory control over tobacco products. In the absence of scientific and technical guidance from WHO, many countries may inadvertently repeat the past mistakes of relying on measurements of tar and nicotine as measures of human exposure and disease risks from tobacco products. The scientific basis for examining emissions, exposures and pathological effects is rapidly evolving with the close prospect of effective strategies for product regulation based on validated scientific methods of testing. During this interval of rapidly changing knowledge, Member States are looking to WHO for scientific and technical guidance on these complex issues.

34. The recommendation enables Member States to be guided in the effective use of resources for meeting the requirements of the Framework Convention, and creates a framework for international cooperation and coordination for product testing. It also cautions Member States about the risks of allowing tobacco-industry sources to fund, support or guide the development of the laboratory capacity required for regulation.

### **Implications for the Organization's programmes**

35. Given the inadequacy of the current methods adopted by the International Organization for Standardization, WHO will continue to support work on improving standards for tobacco-product testing, and to help laboratories for research and testing to anticipate the rapid evolution of products and adjust their procedures accordingly.

36. The diversity of tobacco products marketed and consumed worldwide makes the need for tobacco-product regulation more urgent. WHO will support work to rectify the insufficiency of information about the contents and/or emissions of all tobacco products and to strengthen the regulatory process by broadening it to cover all categories of products. The recommendation adopted by the Study Group provides guidance for expanding laboratory capacity for testing and establishes a framework for support of Member States through the Organization's programmes. To that end, WHO and its partners are establishing a global network of scientists and laboratories concerned with testing of tobacco products, whose members will meet for the first time in April 2005 in the Netherlands.

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