WORLD HEALTH ORGANIZATION

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

Report by the Secretariat

WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Forty-ninth report
Geneva, 19-23 October 1998[2]

Main recommendations

1. The WHO Expert Committee on Biological Standardization reviews developments in the field of biological substances, which include vaccines, blood products and biological therapeutics, and recommends procedures to assure their quality, safety and efficacy, including 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 diagnostic procedures, allows comparability of data globally. Based on the results of international collaborative studies, the Expert Committee established 11 new or replacement international reference materials. Additionally, 11 international reference materials no longer required were discontinued after a recently introduced consultative process. A fully revised and complete list of WHO International Standards and Reference Reagents is published as an annex to the report. The list is also available on the Internet.

3. The Committee also adopted updated requirements for *Haemophilus influenzae* type b conjugate vaccine. These were renamed "Recommendations" to better reflect their nature. WHO Requirements for *H. influenzae* type b conjugate vaccine were first published in 1991. Although these have been valuable, they needed updating to reflect recent developments and advances in vaccine quality control. In particular, the biological assay of potency recommended in 1991 had been shown not to correlate with the efficacy of the vaccine in infants, nor to provide a sensitive indicator of vaccine quality. The Expert Committee therefore agreed that although immunogenicity testing in animals was necessary during vaccine development, an animal immunogenicity test need not be used for routine batch

[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. 897, 2000.

release. Instead, testing should focus on physicochemical tests to monitor consistency of production of the polysaccharide, the protein carrier and the bulk conjugate.

4. An Addendum to the recommendations for oral poliomyelitis vaccine (OPV) was also adopted by the Expert Committee. Great progress has been made in understanding the molecular basis of attenuation and reversion of the Sabin poliovirus strains used for manufacture of OPV. An addition to the existing requirements was made by introducing a new molecular technique, called mutant analysis by polymerase chain reaction and restriction enzyme cleavage (MAPREC), for the quality control of the vaccine. This is the first of a new generation of tests for the molecular consistency of production of live virus vaccine. Other additions adopted were new tests for adventitious agents. Results with these tests have shown that tests on cell cultures had effectively excluded live SV40 from OPV for over 30 years. Newly developed gene amplification tests can also detect noninfectious SV40 sequences. Although there is no evidence of SV40 sequences in OPV, the Expert Committee agreed to the introduction of a gene amplification test for SV40 in poliovirus seed stocks to provide an additional level of security.

Significance for public health policies

5. The increasing complexity and sophistication of biological/biotechnological substances used in human medicine, and the rapid growth in their volume, present a considerable challenge for regulatory authorities, especially in the developing world. The nature of biologicals, and especially novel biotechnology products and procedures, raises particular questions concerning complex issues of quality and safety which require coordinated research and consideration at an international level. WHO has played a key role for over 50 years in establishing international reference materials and in developing recommendations on the production and control of biological substances. Recommendations published by WHO are intended to provide guidance for national regulatory authorities and for manufacturers of biological products. They are adopted by many national authorities as definitive national regulations or as the basis for such national regulations.

6. New assays and biotechnologies, including physicochemical techniques, are also evaluated by the Expert Committee, as appropriate, through collaborative laboratory studies. This is done to develop standardized, validated and robust quality control procedures and criteria for assuring the quality and safety of biologicals and for incorporation into guidance documents. An important development recommended by the Committee is the setting up of an informal working group to develop reference materials for evaluating the prion diagnostic tests that are becoming available. Reliable methods for the accurate diagnosis of bovine spongiform encephalopathy and other human and animal transmissible spongiform encephalopathies are urgently needed.

7. International biological standards and other reference materials are crucial for the standardization, quality control, and safety of biological medicinal products. Many are calibrated in International Units of biological activity, established after extensive international collaborative studies involving many laboratories. These international standards are used to calibrate regional and national working standards, or those of manufacturers; they often form the basis for the licensing of biologicals, and in the case of therapeutics, for clinical dosing. In this way the potency of biological medicinal materials is directly traceable to the WHO International Standard, and are expressed in comparable International Units worldwide.

Implications for the Organization's programmes

8. The Expert Committee on Biological Standardization provides up-to-date recommendations on the quality and safety of biological substances used in medicine, and ensures the availability of necessary international reference materials. Its work enables WHO to fulfil its constitutional responsibilities in this area.

9. The importance of the information and recommendations in the report emphasizes the need for WHO to disseminate widely the recommendations of the Committee to national regulatory authorities, national control laboratories and manufacturers of biologicals. Every effort should also be made to facilitate early access to the Committee's conclusions and recommendations through a summary of information published in the scientific literature.

10. The observations, conclusions and recommendations of the Expert Committee have significant implications for several of WHO's activities. In particular they contribute to provision of timely recommendations and reference preparations for assuring the safety and quality of vaccines, and provision of reference preparations 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 agencies such as UNICEF and WHO.

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Fifty-second report of the Joint FAO/WHO Expert Committee on Food Additives Rome, 2-11 February 1999[1]

Main recommendations

11. The Joint FAO/WHO Expert Committee on Food Additives made recommendations on residues of several veterinary drugs in food of animal origin. The report also contains general consideration of items relating, *inter alia*, to the evaluation of antimicrobial agents, the safety of residues at the injection site, statistical approaches for recommending maximum residue limits (MRLs) for veterinary drugs in food, requirements for the validation of analytical methods, and harmonization with the Joint FAO/WHO Meeting on Pesticide Residues on substances used both as veterinary drugs and as pesticides.

12. The Committee evaluated one β-adrenoceptor-blocking agent (carazolol), one anthelminthic agent (doramectin), four antimicrobial agents (dihydrostreptomycin, streptomycin, neomycin and thiamphenicol), two insecticides (deltamethrin and phoxim), and four production aids (estradiol-17β, progesterone, testosterone, and porcine somatotropins). An analytical method for detecting residues of one tranquillizing agent (azaperone) that had been evaluated at an earlier meeting was also considered. Acceptable daily intakes (ADIs) were established either at the current or previous meetings for all the substances except deltamethrin, for which an ADI was established by the 1982 Joint FAO/WHO

[1] WHO Technical Report Series, No. 893, 2000.

Meeting on Pesticide Residues.[1] MRLs or temporary MRLs were recommended for all these substances either at the present or previous meetings.

13. WHO has published summaries of the toxicological and related information upon which the safety assessments of the veterinary drugs were made.[2] FAO has published summaries of the residue information that formed the basis for the recommended MRLs.[3]

Significance for public health policies

14. The Committee's work emphasizes the public health significance of the risk assessment of chemicals used in food. It highlights the complexity of the process, which includes assembling and analysing all relevant data; interpreting studies of carcinogenicity, genotoxicity, reproductive toxicity, developmental toxicity, antimicrobial activity, and other effects; extrapolating to humans the effects observed in experimental animals; and assessing risks to humans based on available toxicological, epidemiological and microbiological data.

15. Although all Member States face the problem of assessing these risks, only a few scientific institutions can undertake such assessments at this stage. Therefore, it is important to provide all Member States with valid information on both the general aspects of risk assessment and the specific veterinary drugs covered in this report.

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

Implications for the Organization's programmes

17. The evaluation of chemicals in food by the Committee is an ongoing activity. Four meetings are scheduled for the 2000-2001 biennium, two on food additives and contaminants and two on residues of veterinary drugs in food.

18. The Joint FAO/WHO Food Standards Programme acts as the secretariat for the Codex Alimentarius Commission. The Committee's evaluations are crucial to the work of the Commission.

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

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[1] FAO Plant Production and Protection Paper, No. 46, 1983.

[2] *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 43, 2000.

[3] *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/12, 2000.