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

Report by the Secretariat

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirty-sixth report
Geneva, 31 May – 4 June 1999[2]

Main recommendations

1. The report covers the extension and revision of *The international pharmacopoeia*, and the adoption of specifications on drug substances and drug products, together with new International Chemical Reference Substances (now totalling 213) and International Infrared Reference Spectra (now totalling 69). It was proposed that newer techniques (first choice) and less advanced methods be provided in parallel. The Committee emphasized the importance of compliance with pharmacopoeial requirements as part of the overall strategy for detecting counterfeit and substandard products.

2. In relation to *The international pharmacopoeia*, the Committee recommended the use and development of further basic tests for quick screening of drugs, for example at ports of entry, especially for antimalarial and antituberculosis drugs. In total, 345 basic tests exist for pharmaceutical substances, 208 for dosage forms and four for medicinal plant materials.

3. The Committee adopted the revised guidelines on good practices for national pharmaceutical control laboratories. It also suggested the continuation of external quality assessment of analytical results by a limited number of national and regional laboratories. Further guidance on considerations for requesting analysis of drug samples and a Model Certificate for Analysis were also adopted.

[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. 902, 2002.

4. The revised good manufacturing practice (GMP) text for sterile pharmaceutical products was adopted. Promotion of basic elements of GMP to interested parties and decision-makers was encouraged and basic information adopted for use.

5. The Committee adopted draft guidelines on quality systems for GMP inspectorates and on pre-approval inspection.

6. The Committee endorsed activities related to the control and safe trade of starting materials for pharmaceuticals, recommended in the report of a consultation held on the topic,[1] for action by governments, manufacturers, traders and brokers, and by WHO. These would include the drafting of good trading and distribution practices, and of a certification scheme for starting materials moving in international commerce, as requested in resolution WHA52.19. The Committee also endorsed a text relating to packaging materials mainly addressed to those involved in the supply of drugs.

7. The Committee endorsed a system for the selection of comparator products to facilitate the establishment of interchangeability of multisource (generic) pharmaceutical products. The adopted text includes a list of international comparator products and a decision-tree which can help national authorities in assessing the interchangeability of products on their markets.

8. The Committee expressed strong support for the collaboration with the International Pharmaceutical Federation in the development of guidance for good storage practice.

9. The Committee reviewed progress made on drug terminology, particularly in relation to international nonproprietary names (245 proposed and 275 recommended names were newly published), and endorsed the Guidelines on the use of International Nonproprietary Names (INNs) for pharmaceutical substances.

Significance for public health policies

10. Drugs can play a major role in improving human health and promoting well-being only if they are safe and of assured quality. This has been underlined by the repeated occurrence in various countries of cases of poisoning with diethylene glycol. Vigorous implementation of good manufacturing practices in the local production of pharmaceuticals is the first prerequisite for prevention. However, as proposed by the Committee, international agreements should also be considered in order to strengthen preventive measures.

11. Special efforts have been undertaken to raise awareness of the need for regulatory measures covering the safety of, and trade in, starting materials – including active pharmaceutical ingredients and excipients – and for implementation of good manufacturing practices. The participation and support of policy-makers and the entire public health community are required, involving both the public and private sectors.

12. Evidence shows, however, that problems regarding the quality assurance of pharmaceuticals persist. This applies especially to the growing incidence worldwide of production, distribution and sale of counterfeit, spurious and substandard pharmaceutical products. A waste of money for the people who buy them, counterfeit and substandard drugs prolong treatment periods, exacerbate the conditions being treated, help create drug resistance and can even cause death. The statutory instruments, advice

[1] Document WHO/PHARM/98.605.

and recommendations provided in the Committee's report can help national authorities – in particular drug regulatory authorities – to combat these problems.

Implications for the Organization's programmes

13. The Organization should continue to promote a comprehensive approach to quality assurance of pharmaceutical products. Similarly, it should lead and coordinate international efforts to define and harmonize clear and practical standards and guidelines for pharmaceuticals, particularly in response to increased trade.

14. Although the Organization seeks to enhance the rational use of scarce resources and consumers' confidence in health care, its priority objective remains to ensure the safety, efficacy and quality of medicinal products for maintaining and improving public health.

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Fiftieth report
Geneva, 25-29 October 1999[1]

Main recommendations

15. 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.

16. 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 28 new or replacement international reference materials. Additionally, a number of international reference materials no longer required were disestablished. An up-to-date list of WHO International Standards and Reference Preparations is available on the Internet.[2]

17. The Expert Committee adopted an amendment to the requirements for meningococcal polysaccharide vaccine, an addendum to the guidelines for the development of standards and reference reagents for biological substances, and a decision-tree for setting priorities in the development of such reference materials.

18. The Committee also adopted a major revision and updating of WHO's recommendations for oral poliomyelitis vaccine. WHO's requirements for oral poliomyelitis vaccine were last revised in 1989. Since that time new quality control tests had been developed that introduced significant changes in the control of the vaccine. A test called mutant analysis by polymerase chain reaction and restriction enzyme cleavage (MAPREC) is included in the updated recommendations as an additional test for the

[1] WHO Technical Report Series, No. 904, 2002.

[2] http://www.who.int/biologicals

consistency of production of poliovirus type 3. This is the first of a new generation of tests for the molecular consistency of a live virus vaccine.

19. The discovery of the gene for the cellular receptor for poliovirus had led to the development of transgenic mice that, unlike normal mice, were susceptible to poliovirus infection. A neurovirulence assay for poliovirus vaccine had been developed and validated in a transgenic mouse line and the Expert Committee agreed to its introduction as a suitable alternative to the neurovirulence test carried out in primates for type 3 poliovaccine.

20. The updated recommendations for oral poliomyelitis vaccine also include changes to improve the monitoring and exclusion of adventitious agents.

Significance for public health policies

21. The increasing complexity and sophistication of biological and biotechnological substances used in medicine present a considerable challenge for regulatory authorities, especially in the developing world. WHO plays a key role in establishing international reference materials and in drawing up recommendations on the production and control of these biological substances. 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 manufacturing standards and often form the basis for licensing, routine lot release and clinical dosing worldwide.

22. The Expert Committee evaluates new assays and biotechnologies as appropriate through collaborative studies. This enables it 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. The entire cycle in the development of the MAPREC assay and the transgenic mouse model for assessing oral poliomyelities vaccine, from basic scientific research, through method development, to standardization and application as control tests, is a paradigm for regulatory research. The work clearly illustrates the need for long-term commitment of resources in order to make significant advances in the control and standardization of biologicals.

23. The new quality-control procedures for oral poliomyelitis vaccine have the potential to increase the stringency of control of the vaccine. This is an important consideration, as the risks and benefits of using the vaccine are changing as a result of the success of the poliomyelitis eradication programme. Furthermore, use of the new quality-control procedures has the potential to reduce the time needed to complete the testing of the vaccine and to make it available more quickly. As demand for the vaccine is higher than ever, any procedures that shorten the supply time were to be welcomed. Significantly, the MAPREC test does not require the use of infectious wild-type poliovirus as control, unlike previously used testing procedures. Thus, the new recommendations also contribute to increased biosafety during testing of the vaccine.

Implications for the Organization's programmes

24. 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.

25. 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 be made to ensure early access to the Committee's conclusions and recommendations through publication of a summary of the information in the scientific literature and dissemination of relevant information on the Internet.

26. The observations, conclusions and recommendations of the Expert Committee on Biological Standardization 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 plasma products. The global norms and standards defined by the Committee provide the basis for assessing the acceptability of vaccines for purchase by WHO and other international organizations, such as UNICEF.

27. In order to assure a smooth and effective adoption of the new recommendations for oral poliomyelitis vaccine, interested parties should be advised of the decisions of the Expert Committee. A programme should be set up to implement the MAPREC and transgenic mouse assays, which should include a training component.

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Fifty-first report
Geneva, 30 October – 3 November 2000[1]

Main recommendations

28. Based on the results of international collaborative laboratory studies, the Expert Committee established six new or replacement international reference materials. Additionally, one international reference material was re-established, three were renamed and one preparation no longer required was discontinued.

29. The Expert Committee adopted revised recommendations for the production and quality control of inactivated poliovirus vaccine, new Guidelines for the production and control of Japanese encephalitis vaccine (live) for human use, and a revised addendum to the recommendations for oral poliomyelitis vaccine.

30. The Expert Committee was informed of discussions that had taken place at a WHO Consultation on International Biological Standards for *in vitro* Diagnostic Procedures (September 2000). International biological standardization is becoming increasingly important for the regulation of clinical diagnostic procedures and the consultation was the first occasion at which participants from various disciplines had met together to discuss issues associated with the provision of international reference materials in this area. The Expert Committee recommended that WHO should collaborate closely with the International Standards Organization and other scientific bodies with interest in the *in vitro* diagnostic field to ensure that the distinct characteristics and difficulties of standardization of biological diagnostic reagents are clearly recognized.

[1] WHO Technical Report Series, No. 910 (in print).

Significance for public health policies

31. Japanese encephalitis is a major cause of viral encephalitis in the Asia and Pacific areas. A live attenuated vaccine has been developed in China where it has been licensed and used for a number of years as an alternative to existing inactivated vaccines. Several countries are interested in using the live attenuated vaccine. The new guidelines for live attenuated Japanese encephalitis vaccine provide information and guidance concerning the history, characteristics, production and control of live attenuated Japanese encephalitis vaccine and are designed to facilitate progress towards the eventual international licensure of the vaccine.

32. WHO recommendations for oral poliomyelitis vaccine were revised to introduce the use of transgenic mice as an alternative to the neurovirulence test in primates for types 1 and 2 poliovaccine. This decision extends a previous decision of the Expert Committee to establish the transgenic mouse test for type 3 poliovaccine. The public health implications of this decision are increased flexibility in testing options for poliovaccine, without any compromise on quality.

Implications for the Organization's programmes

33. Continuing concerns about the quality and safety of plasma-derived medicinal products have resulted in a number of urgent requests from Member States for support and advice from WHO, in addition to the requests set out in resolution WHA50.20 (1997) on the quality of biological products moving in international commerce. The development of the guidelines on viral inactivation is a part of the response to the requests.

34. The introduction of the transgenic mouse assay for oral poliovaccine has implications for the eradication of poliomyelitis. It would be necessary for laboratories intending to use the new assay to follow standard training and implementation procedures. A programme of training and staged implementation has been developed by WHO in order to facilitate the introduction of the new assays.

35. In the area of *in vitro* diagnostics the Expert Committee recommended that WHO should clarify issues of terminology and nomenclature, and improve communication so that respective responsibilities towards medical, academic research, and diagnostic professionals are understood and recognized.

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Fifty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives Rome, 21-27 February 2002[1]

Main recommendations

36. The Committee made recommendations on residues in food of animal origin of several veterinary drugs. The report also contains general consideration of items relating to risk assessment principles, the Project to update principles and methods for the risk assessment of chemicals in food, and risk assessment practices. As part of the reviews of the antimicrobial agents, a decision-tree for

[1] WHO Technical Report Series, No. 911, 2002.

determining adverse microbiological effects of residues of antimicrobial drugs in food-producing animals was developed.

37. The Committee evaluated three anthelminthic agents (doramectin, ivermectin, and tiabendazole), seven antimicrobial agents (cefuroxime, dihydrostreptomycin, streptomycin, lincomycin, neomycin, oxytetracycline, and thiamphenicol), four insecticides (cyhalothrin, cypermethrin, *alpha*-cypermethrin, and phoxim), and one production aid (melengestrol acetate). Acceptable daily intakes (ADIs) or temporary ADIs were established either at the current or previous meetings. Maximum residue limits (MRLs) or temporary MRLs were recommended for all of these substances either at the present or previous meetings, except for thiamphenicol, for which the temporary MRLs in muscle, liver, kidney and fat of pigs and muscle of fish were not extended because the information requested at the Committee's fifty-second meeting (Rome, 1999) was not available.

38. WHO has published summaries of the toxicological and related information upon which the safety assessments of the veterinary drugs were made.[1] FAO has published summaries of the residue information that formed the basis for the recommended MRLs.[2]

Significance for public health policies

39. 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, teratogenicity, etc.; extrapolating to humans the effects observed in experimental animals; and characterizing hazards to humans based on available toxicological and epidemiological data.

40. Although all Member States face the problem of assessing potential risks of chemicals in food, only a few scientific institutions can assess the relevant toxicological and related data at this stage. It is therefore important to provide Member States with valid information on both the general aspects of risk assessment and specific veterinary drugs covered in this report.

41. 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 and have been allocated an ADI. This ensures that food commodities in international trade meet strict safety standards.

Implications for the Organization's programmes

42. The Joint FAO/WHO Expert Committee on Food Additives continually evaluates chemicals in food. Four meetings are scheduled for 2003-2004: two on food additives and contaminants, one on contaminants, and one on residues of veterinary drugs in food.

43. 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 that of the Commission.

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

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[1] *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 49, 2002.

[2] *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper, No. 41/14.

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Fifty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives Geneva, 4-13 June 2002[1]

Main recommendations

45. The Committee evaluated the following food additives using normal toxicological procedures: the sweetening agent alitame, the excipient cross-linked sodium carboxymethyl cellulose, mineral oils, the low-calorie fat salatrim, and nitrate and nitrite (as food additives, natural constituents, and contaminants). Amyloglucosidase from *Aspergillus niger*, was considered for specifications only.

46. The Committee reviewed the heavy metals and arsenic limits of 52 colours and 44 acidity regulators.

47. The Committee evaluated 196 flavouring agents in six chemical groups using the Procedure for the Safety Evaluation of Flavouring Agents. On the basis of the toxicological, metabolic, and intake data on these flavouring agents and their structural characteristics, the Committee concluded that all of them were of "no safety concern". Sixty-seven additional flavouring agents were considered for specifications only.

48. The Committee evaluated secondary components of 51 flavouring agents (for which the minimum assay figures were below 95%) and concluded that the secondary components do not raise safety concerns and confirmed its conclusions that the secondary components of 63 flavouring agents, including those from previous evaluations, do not present any safety concern at the current estimated levels of intake. The specifications for the 51 flavouring agents will be reviewed at a future meeting.

49. The Committee evaluated 18 flavouring agents that it had not been able to evaluate at its fifty-seventh meeting (Rome, 2001) because of the lack of information on whether they were in current use as flavouring agents. On the basis of additional information, the Committee determined that 16 of these were of "no safety concern". The evaluations of glycerol and propylene glycol stearate were not finalized, pending development of the definition of "flavouring agent".

50. Summaries of the toxicological and related information which served as the basis for the Committee's evaluations of the safety of these food additives will be published separately by WHO.[2] Specifications will be published by FAO.

51. The report also contains general consideration of items relating to risk analysis, exposure assessment and the Project to update the principles and methods for the risk assessment of chemicals in food.

Significance for public health policies

52. As noted in paragraphs 39 to 41 above, it is important that Member States are provided with valid information on both the general aspects of risk assessment and specific food additives and contaminants so that risks can be assessed at national level.

[1] WHO Technical Report Series, No. 913, 2002.

[2] *Safety evaluation of certain food additives*, WHO Food Additives Series, No. 50, in press.

53. International food standards are established only for substances that have been evaluated by the Committee and have been allocated an ADI (food additives) or for which a tolerable intake level has been established or potencies have been estimated (contaminants).

Implications for the Organization's programmes

54. Implications of the Committee's work for WHO's programmes are indicated in paragraphs 42 to 44, above.

WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Thirty-third report
Geneva, 17-20 September 2002[1]

Main recommendations

55. Since its first meeting in 1949, the WHO Expert Committee on Drug Dependence has regularly reviewed medical and scientific information on psychoactive substances and recommended their scheduling under the relevant international drug control conventions. Bearing in mind the scheduling criteria spelled out in the Guidelines for the WHO review of dependence-producing psychoactive substances for international control,[2] the Committee reviewed the following five substances at its latest meeting: amfepramone, amineptine, buprenorphine, *delta*-9-tetrahydrocannabinol and tramadol. Of these, amineptine and tramadol were assessed in the context of new scheduling and the remaining three substances were reviewed to determine whether a change in their current scheduling status would be needed. The Committee recommended amineptine for inclusion in Schedule II, and *delta*-9-tetrahydrocannabinol for transfer from Schedule II to Schedule IV, both of the 1971 Convention on Psychotropic Substances. The Committee did not make scheduling recommendations with respect to the remaining three substances, but recommended that WHO keep tramadol under surveillance.

56. The Committee also pre-reviewed six substances and selected butorphanol, ketamine, khat (*Catha edulis*) and zopiclone for future review. Not selected for future review were oripavine and zaleplon.

57. In the course of reviewing these substances, the Committee identified two gaps in the Guidelines mentioned above: the Committee urged WHO to develop additional scheduling guidelines in consultation with appropriate bodies of the United Nations for clarifying issues related to the control of (a) the substances having some similarity to both narcotic drugs and psychotropic substances, and (b) the substances which are convertible into narcotic drugs.

58. Historically, this Committee has been instrumental in the development and clarification of the concept of "drug dependence". At its latest session, the Committee reviewed terminology used in reporting abuse-related adverse drug reactions to psychoactive medicines, and noted that withdrawal from selective serotonin reuptake inhibitors was a problem in some patients. The Committee recommended that such inhibitors should be placed on the agenda of the next Committee for

[1] WHO Technical Report Series, No. 915, 2003.

[2] Document EB105/2000/REC/1, Annex 9.

consideration, not in the context of control, but to promote education and information on the appropriate use of psychoactive drugs.

Significance for public health policies

59. In accordance with the Guidelines mentioned above, the resultant recommendations concerning the international control of amineptine was posted on the Internet[1] and communicated to the United Nations for review by the Commission on Narcotic Drugs. This decision-making mechanism is intended to allow the timely updating of the list of controlled drugs in order to keep the international drug-control system responsive to the changing patterns of drug use and abuse. Recommendations by the Committee regarding *delta*-9-tetrahydrocannabinol were not referred by the Director-General to the Commission and they will be reviewed with respect to possible consideration in 2004.

60. The identification of the two gaps in the Guidelines and the recommendation to draw up additional guidance to cover them will further promote clear rules for the WHO review of dependence-producing psychoactive substances. Clearer rules will, in turn, increase the openness and transparency with which WHO undertakes the review and may contribute to better acceptance of its outcome.

61. Clarification of the terms used in reporting abuse-related adverse drug reactions to a broad range of psychoactive medicines, including selective serotonin reuptake inhibitors, is expected to promote the reporting of abuse-related adverse drug reactions, to foster the rational selection and use of psychoactive medicines, and to stimulate research in this area.

Implications for the Organization's programmes

62. The selection of the four substances for future review by the Committee indicates the need for WHO's continuing contribution in the area of international drug control.

63. A working group has been convened for drafting the supplementary guidelines for the WHO review of dependence-producing psychoactive substances for international control. Pending clarification from the United Nations Office on Drugs and Crime on some outstanding questions, it is expected that these guidelines can shortly be finalized and submitted to the Executive Board for its consideration.

64. In the past, drug dependence tended to be discussed primarily in the context of drug control. The discussion of abuse-related adverse drug reaction terms by this Committee has indicated the need for further consideration of withdrawal and dependence experienced in the course of therapeutic use of a wide range of psychoactive medicines. This may lead to the identification of new informational or educational activities in the context of rational selection and use of psychoactive medicines.

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[1] http://www.who.int Search the word "narcotic"; open first activity listed.