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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirty-sixth Report

World Health Organization
Geneva

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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 31 May–4 June 1999

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 31 May to 4 June 1999. The meeting was opened on behalf of the Director-General by Dr M. Scholtz, Executive Director of Health Technology and Pharmaceuticals, who stressed that it was of the utmost importance that WHO should vigorously maintain and strengthen its constitutional responsibility for setting clear and practical norms if it was to meet the needs and expectations of its 191 Member States. Essential drugs were recognized as a high priority, but WHO also needed to maintain all its activities concerned with drugs, including innovative products. A crucial part of the quality assurance programme was the network of 13 WHO collaborating centres, whose activities included the verification of test methods, the establishment of reference materials, and training. During the World Health Assembly in May 1999, concern had been expressed about persistent problems in ensuring the quality of medicines and their starting materials. Member States were urged to establish and enforce regulations to ensure quality assurance of pharmaceuticals, and WHO was called on to extend guidelines incorporated in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*1*) to cover pharmaceutical starting materials. WHO was also called on to develop further training tools for inspectors to ensure compliance with good manufacturing practices (GMP) published by WHO.

Dr Scholtz also emphasized the importance of the links between the setting and the implementation of normative standards, and urged the Expert Committee to keep those links in mind throughout its discussions.

The Ninth International Conference of Drug Regulatory Authorities (ICDRA), held in Berlin in April 1999, had reviewed progress made in the international harmonization of regulatory requirements, and the collaboration between WHO and the International Conference on Harmonisation (ICH). WHO's role was to ensure that the advantages of harmonization were of benefit to all concerned (as endorsed by the World Health Assembly in resolution WHA45.28; *2*).

Dr J.D. Quick, Director, Essential Drugs and other Medicines, briefed the Committee on the new headquarters structure of WHO, and outlined new challenges for WHO in the area of pharmaceuticals and biologicals. These included, inter alia, increased internationalization of the trade in, and production of, starting materials, intermediates and finished products. A matter of serious concern was that drugs

of poor quality that were ineffective and harmful remained on sale. Only one-sixth of the 191 WHO Member States had well-developed capacities for drug regulation. WHO's strategies to meet these challenges included the provision of global guidance by means of internationally applicable norms and standards, and the strengthening of national drug regulation (through, for example, guidelines, manuals and training on GMP, laboratory practices, inspection and registration). WHO facilitated communication and information exchange through newsletters and bodies such as the Association of South-East Asian Nations (ASEAN) and the African Drug Regulatory Authorities Network (AFDRAN), and provided a forum for regulators.

Dr J. Idänpään-Heikkilä, Special Adviser on Quality Assurance and Safety within Health Technology and Pharmaceuticals, informed the Committee of the progress made in drug quality assurance since its last meeting. Because of the concern that exists regarding the control of starting materials, a meeting was held in 1998 at which proposals were made for a model certificate of analysis, and for expansion of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce to include starting materials, as well as brokers and traders in such materials (*3*). Efforts to enhance the implementation of GMP and to create an awareness of the need to produce good quality products, as well as the preparation of training modules for GMP inspectors, were also proposed.

A list of international comparator products, together with guidance on how best to choose such a product for the purpose of assessing interchangeability, had been drafted in collaboration with drug regulatory authorities and the pharmaceutical industry. This list was presented to the Committee, which was asked to consider its adoption. Collaboration with the World Intellectual Property Organization (WIPO) for the protection of International Nonproprietary Names (INNs) had also been strengthened. The Committee was further informed that WHO retained its observer status in ICH and continued its role in ICDRA.

2. Quality control — specifications and tests

2.1 *The international pharmacopoeia* — 50 years on

The Committee confirmed that publication of *The international pharmacopoeia* (*4*) continued to fulfil a need in developing countries by providing less technically advanced tests for specific substances and preparations. The usefulness of monographs for finished products was also confirmed.

The Committee discussed the merits of introducing modern analytical techniques. It was recognized that such new techniques could sometimes be more sensitive, rapid and robust, as well as potentially less expensive. However, there was still a need for less advanced methods. It was proposed that information on both types of methods might be provided in parallel, with the newer techniques indicated as the first choice and the less advanced methods as alternatives. Thus, where resources permitted, the more technically advanced methods should be used. However, the possibility of using the less advanced alternative methods to check compliance with pharmacopoeial specifications, where necessary, would increase the usefulness of *The international pharmacopoeia*. In making these proposals, the Committee emphasized the importance of compliance with pharmacopoeial requirements as part of the overall strategy for detecting counterfeit and substandard products (5). The introduction of alternative methods would require careful presentation, and it was recommended that a statement should be inserted in Volume 5 of *The international pharmacopoeia* to introduce the concept, together with the use of appropriate headings. This would reiterate that implementation of *The international pharmacopoeia* was the responsibility of national drug authorities.

2.2 Monographs for *The international pharmacopoeia*

The Committee was pleased to note that a number of additional monographs for drug substances, pharmaceutical preparations (e.g. tablets) and excipients are nearing completion for inclusion in *The international pharmacopoeia*. It approved the inclusion of monographs for antimalarials in Volume 5 of *The international pharmacopoeia*, which is currently in press.

2.3 Dissolution test requirements for individual monographs

The Committee was informed that the WHO collaborating centres were assisting with proposals on work in establishing dissolution requirements, test conditions and acceptance criteria (limits) for certain monographs. The Committee supported the concept of cooperation with the International Pharmaceutical Federation (FIP) in hands-on courses on dissolution testing. It is envisaged that WHO collaborating centres might provide a venue for such courses and that attendance would be open to participants from national control laboratories and the pharmaceutical industry.

2.4 Basic tests for pharmaceutical substances and dosage forms

The Committee was informed of progress in the development of basic tests, and verification by the collaborating laboratories. So far, three

volumes (*Basic tests for pharmaceutical substances, Basic tests for pharmaceutical dosage forms* and *Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms* (*6–8*)) have been published. These volumes now include 345 basic tests for substances, 208 for dosage forms and four for medicinal plant materials. The next volume will be made available once a sufficient number of tests have been developed and verified.

The need for four verifications of each test for dosage forms as currently applied according to Annex 6 of the Committee's twenty-ninth report (*9*) was discussed. The possibility of accepting three verifications was suggested, provided that there were no significant differences between the results. The use of additional laboratories, and encouraging feedback from those using the tests, was advocated.

3. Quality control — reference materials

3.1 International Chemical Reference Substances

The 1997 and 1998 reports of the WHO Collaborating Centre for Chemical Reference Substances were presented to the Committee. Nine new International Chemical Reference Substances (ICRS)[1] were adopted by the Committee according to the procedure described in its thirty-second report (*10*). The recommendation to withdraw the reference substance for tubocurarine hydrochloride was endorsed since it is no longer required. The total collection now comprises 205 chemical reference substances and 12 melting-point reference substances (Annex 1).

The Committee adopted the reports and expressed its appreciation to the WHO Collaborating Centre for Chemical Reference Substances for its work, and to the National Corporation of Swedish Pharmacies for its continued financial support to the WHO programme on ICRS.

3.2 International Infrared Reference Spectra

A total of 69 International Infrared Reference Spectra (IIRS) are currently available from the WHO Collaborating Centre for Chemical Reference Substances, Kungens Kurva, Sweden (Annex 2). The Committee acknowledged the contribution of the WHO Collaborating Centre for International Infrared Reference Spectra, Zurich,

[1] Captopril, captopril disulfide, ciprofloxacin hydrochloride, cisplatin, kanamycin monosulfate, piperazine adipate, piperazine citrate, sodium amidotrizoate and streptomycin sulfate.

Switzerland, which prepares the spectra. It was agreed that in future the infrared reference spectra would be recorded on a Fourier transform infrared spectroscopy instrument and that they should be published in reduced size, either in *The international pharmacopoeia* or as a separate publication.

3.3 Biological reference materials

The Committee noted that the WHO Expert Committee on Biological Standardization was carrying out a review of biological reference materials. Any such materials proposed for discontinuation as a biological reference material would be assessed by the WHO Collaborating Centre for Chemical Reference Substances for its potential suitability for use as an ICRS.

3.4 Information on reference materials for pharmacopoeial analysis

The Committee noted that the comprehensive list of reference substances and infrared reference spectra is regularly updated and available on the Internet at http://www.who.int/medicines.

4. Quality control — pharmaceutical control laboratories

4.1 Good practices for national pharmaceutical control laboratories

The Committee adopted the revised guidelines (*11*) on good practices for national pharmaceutical control laboratories (GPCL) (Annex 3). The new title was chosen to emphasize that these guidelines were intended primarily for national control laboratories. They take into account other existing guidance on the subject, including that provided by the International Organization for Standardization (*12*), the Organisation for Economic Co-operation and Development (*13*) and the Swiss Association for Standardization (*14*), as well as the recommendations on a quality system for official medicines control laboratories, published by the Pharmaceutical Inspection Convention (PIC) (*15*).

The importance of these guidelines should be drawn to the attention of the national drug control authorities that would be responsible for their implementation. It should be noted that a model test report for active pharmaceutical ingredients, excipients and medicinal products is appended to the guidelines.

4.2 Equipment for drug control laboratories

The Committee adopted a revised list of equipment for pharmaceutical control laboratories to be appended to the GPCL (see Annex 3). National control laboratories may contact the WHO Secretariat for detailed information on costs.

4.3 Requests for analysis of drug samples

The Committee adopted recommendations to countries which need to request the analysis of drug samples, e.g. where a national control laboratory does not exist, or where it lacks competence in a particular technique. These recommendations (Annex 4) are applicable to drug regulatory authorities but may also be suitable for the independent analysis of pharmaceuticals in trade.

4.4 External quality assessment

The Committee was informed that, since its previous meeting, 12 national quality control laboratories had been identified and had agreed to participate in a pilot external quality assessment programme. Progress would be reported at its next meeting.

5. Quality assurance — good manufacturing practices

5.1 Good manufacturing practices in pharmaceutical production

The Committee acknowledged the importance of putting norms and standards into practice. If GMP are to be implemented in countries, decision-makers at all levels in the national public health sector must be properly informed about them and convinced of their importance.

Information on the progress made with the project on the implementation of GMP in Member States was reported. Training material on basic GMP principles had been prepared and training modules for advanced GMP topics were planned. It was anticipated that the project would include initial consultation, review and planning; the preparation of training modules; country visits and training in the performance of GMP inspections; the preparation of advanced training modules in validation, water supply and sterile product manufacture; and follow-up workshops. The possibility of establishing training networks was considered, in order to establish a training cascade, i.e. to train trainers, who in turn would train others.

The objective of the project was to improve the implementation of GMP in countries. The selection criteria to be met by the countries

involved included their willingness and commitment to participate, and the presence of local and multinational pharmaceutical manufacturers.

The Committee endorsed the project and encouraged the Secretariat to continue work in this area.

Information on the basic elements of GMP in pharmaceutical production is needed by interested parties and decision-makers at all levels, and the provision of such information is encouraged. A brief summary, intended mainly for non-specialists, is given in Annex 5.

5.2 Good manufacturing practices for sterile pharmaceutical products

A revised text for the section of the GMP guidelines dealing with sterile products (*16*, section 17) was adopted (Annex 6). This took account of the European and other guidelines (*17*, *18*) and comments received, which supported harmonization.

5.3 Guidelines for good storage practices

The Committee encouraged the Secretariat to collaborate with FIP on guidelines for good storage practices. It was noted that a draft prepared by FIP was already available.

5.4 Hazard analysis and critical control point system

A system known as the hazard analysis and critical control point system (HACCP) was brought to the attention of the Committee. While to date HACCP has been used primarily to assess hazards associated with the production of food, it was recognized that the identification of risks and critical processes is part of GMP. The Secretariat was encouraged to explore and make use of appropriate HACCP documentation that might be useful to illustrate the concepts of GMP.

6. Quality assurance — inspection

6.1 Pre-approval inspections

The Committee adopted the guidelines on pre-approval inspections (Annex 7) which extend the advice provided in the provisional guidelines on the inspection of pharmaceutical manufacturers in Annex 2 of its thirty-second report (*19*). Conducting inspections before granting marketing authorization could avoid problems at a later stage in the evaluation process. This should assist both regulatory authorities and manufacturers.

6.2 Quality systems for national GMP inspectorates

The Committee adopted the guidelines given in Annex 8, which are based on PIC recommendations for PIC Contracting States (*20*). Recommendations and requirements for quality systems for the operation of inspection services within a competent authority concerned with GMP inspections are given, relating to administrative structure, organization, personnel, records, inspection procedures, confidentiality and internal audits. These guidelines are intended for use by inspection services as the basis for developing their own quality systems.

7. Quality assurance — packaging

7.1 General aspects of packaging

The Committee adopted a text relating to packaging material which is addressed mainly to those involved in the supply of pharmaceuticals, but also contains important information and references for their development, manufacture and quality control (Annex 9). It focuses on the role of packaging in relation to the stability of pharmaceuticals and the potential for counterfeiting. The objective is to ensure that medicines arrive safely in the hands of the patients for whom they are intended.

7.2 Glass containers for pharmaceutical use and rubber closures for containers of pharmaceuticals

The Committee approved two texts for inclusion in *The international pharmacopoeia*. They provide information on the types and use of glass containers and rubber closures for pharmaceutical purposes.

8. Quality assurance — general topics

8.1 Starting materials for pharmaceutical products: control and safe trade

Further to the discussion during the thirty-fifth meeting of the Committee (*21*) on pharmaceuticals contaminated with diethylene glycol, several activities aimed at ensuring the control of, and safe trade in, starting materials for pharmaceutical products have been identified. The Committee was informed of the report and recommendations of a meeting on this subject that had been held in Geneva in May 1998 (*3*). The Committee noted that the World Health Assembly had adopted the proposed resolution on the revised drug strategy

(WHA52.19) in May 1999 (*22*). Efforts were needed to promote increased awareness of existing guidelines. The Committee noted that several recommendations were made in the report for action by governments, manufacturers, traders and brokers, as well as by WHO, which would need to collaborate with all the parties involved. It was suggested that the above-mentioned recommendations should be consolidated and priorities assigned, and the resulting document circulated widely among associations and representative bodies.

8.2 Model certificate of analysis for use in trade and procurement

A model certificate of analysis was adopted (Annex 10) for use in trade in starting materials and for manufacturers of pharmaceutical substances, excipients and medicinal products, as recommended by World Health Assembly resolution WHA52.19 (*22*).

8.3 Screening tests for antimalarials and antituberculosis drugs

In view of the high priority of WHO's Roll Back Malaria and Stop TB programmes, the Committee emphasized the importance of the different projects being conducted in a number of Member States aimed at developing methods for the rapid detection of counterfeit and substandard drugs. These would be a useful supplement to the WHO basic tests (*6–8*). In particular, it was agreed that thin-layer chromatography (TLC) was a useful method for the rapid screening of pharmaceuticals.

In line with established practice in *The international pharmacopoeia* and the basic tests, the use of hazardous solvents such as chloroform and ether should be avoided, and an effort should be made to minimize the quantities of any solvents used. This is consistent with current safety and environmental considerations.

For both the malaria and tuberculosis programmes, the Committee encouraged the preparation of test manuals to incorporate all relevant tests focused on the particular drug groups concerned. Such manuals should reflect the stepwise approach of progressing first from basic tests to screening methods and then to full pharmacopoeial analysis.

8.4 Tuberculosis programme — fixed-dose combinations

The Committee was informed of WHO treatment policies for tuberculosis aimed at preventing acquired drug resistance and taking into account the most efficient use of limited resources for combating the disease. The key element is the development and promotion of