WHO Technical Report Series
902

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirty-sixth Report

World Health Organization
Geneva

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Contents

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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

fixed-dose combination (FDC) tablets to replace single drug tablets for the treatment of tuberculosis. FDC tablets simplify drug management, treatment (increased patient and doctor compliance) and distribution. Problems possibly associated with FDC tablets include the management of side-effects, stability, the lack of standardization and the poor bioavailability of rifampicin.

It was recommended that the Secretariat should take advantage of the expertise of the Committee to provide advice on the quality assurance aspects of FDC tablets. While appreciating the urgency with which an adequate supply of FDC tablets is required, the Committee emphasized that quality assurance should not be compromised. Attention should be paid to the pharmaceutical aspects of such tablets, particularly their stability and in vitro dissolution. The development of monographs on FDC tablets for *The international pharmacopoeia* was recommended.

8.5 Comparator products for equivalence assessment of interchangeable multisource (generic) products

In line with the recommendations made at its previous meeting (*21*), the Committee adopted the document on "comparator products" (Annex 11). This contains a list of international comparator pharmaceutical products for the equivalence testing and assessment of interchangeable multisource (generic) products and includes a decision-tree for use in identifying comparator pharmaceutical products. It was emphasized that the list was intended to serve as an information tool for drug regulatory authorities and pharmaceutical manufacturers. The suggested use of comparator products is not in any way intended to be binding on those responsible for choosing a reference product. The final decision must be made at the national level. The list and the guidance provided will need to be updated periodically.

8.6 Measures to combat counterfeit drugs

The Committee noted that the guidelines for the development of measures to combat counterfeit and substandard products are approaching finalization. It emphasized the importance of communication among all the bodies involved.

Vigilance and the reporting of counterfeit drugs were necessary at all times, rather than only in response to isolated incidents or when special requests for information were made. The Committee encouraged the sharing of information by national regulatory authorities through the network of liaison officers established to combat counterfeit pharmaceuticals.

8.7 Information on general publications

The Committee noted that the Secretariat maintains a number of useful information resources and databases, including WHO drug quality control data, an index of pharmacopoeias, a list of GMP, monographs of national and regional pharmacopoeias, and official compendia. It was suggested that the Secretariat should explore the feasibility of making these more widely available, possibly in electronic form.

Publications (in English, French and Spanish) are available, inter alia, on basic tests for pharmaceutical substances, dosage forms and medicinal plant materials (*6–8*). It was noted that the texts on some basic tests have also been translated into Chinese.

The Committee noted that Volume 1 of a compilation of various guidelines from previous WHO technical reports has been published under the title *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials* (*23*), and that Volume 2, which contains GMP reports and inspection guidelines, is expected to be published shortly.[1] However, Volume 3 has not yet been planned as compilation will depend on the approval and adoption of reports. Continuation of this work is encouraged to ensure that any changes and additional information will be widely available.

The Committee also noted that the tenth cumulative list of INNs for pharmaceutical substances, which includes all INNs published to date, is being prepared.

9. Nomenclature and computerized systems

9.1 International Nonproprietary Names for pharmaceutical substances

The Committee endorsed the guidelines on the use of INNs for pharmaceutical substances (Annex 12).

The Committee was informed of the current activities of the programme on INNs for pharmaceutical substances. Since it last met, 245 new names have been published as proposed INNs, and 275 names have reached recommended INN status. The Committee was

[1] *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection.* Geneva, World Health Organization, 1999.

pleased with the progress made with regard to the use of INNs in Chinese and Russian.

The revision of the procedure for the selection of INNs will attempt to cover aspects such as objections raised to a proposed INN and the replacement of a recommended INN. New developments in naming biotechnology-derived products are also receiving attention. The Committee endorsed the close collaboration with the WHO Expert Committee on Biological Standardization.

Closer collaboration with WIPO in the field of protection of INNs has been initiated. WIPO's Standing Committee on the Law of Trademarks, Industrial Designs and Geographic Indications has discussed the issue of trademarks and INNs and agreed to conduct a survey to enquire to what extent national patent offices examine trademarks for potential conflict with INNs. Another area of collaboration is with the Internet Corporation for Assigned Names and Numbers (ICANN) in the protection of INNs against misuse in Internet domain names.

9.2 Regulatory information systems

The Committee supported the investigation undertaken to assess the feasibility of establishing information systems linking drug regulatory authorities with WHO, and considered that such systems would be a useful asset. National drug regulatory authorities should be alerted to the possibility that a global information system may be established by WHO in order to avoid problems of duplication or incompatibility.

9.3 Drug quality assurance terminology

As a first step towards greater harmonization, the establishment of a glossary of existing terminology was suggested. While maintaining an awareness of other harmonization initiatives is necessary, the first priority should be to ensure consistency within WHO documents. Many of the basic terms and concepts used in quality assurance are the same for biologicals and pharmaceuticals.

10. Regulatory issues

10.1 Harmonization of regulatory requirements

The Committee noted the accelerating pace of regional and interregional harmonization activities, particularly those under the auspices of ICH. Recognizing WHO's international normative responsibilities, the Committee strongly supported WHO's active participation in such activities. This would facilitate the wider dissemination of

harmonization proposals and consideration of their applicability to the regulatory situations in Member States at different stages of development. While WHO was encouraged to take account of interregional guidelines, the Committee emphasized the need to use these flexibly when formulating WHO recommendations. The latter should be appropriate for use in the context of the broader constituency of WHO's 191 Member States.

The Committee endorsed the recent ICDRA recommendation of April 1999 that WHO should focus, in particular, on the quality and regulation of multisource (generic) medicinal products. It urged the Secretariat to take measures to make its international normative function more widely known and understood, and to provide information on its participation in other harmonization activities.

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WHO Technical Report Series, No. 902, 2002

Annex 1
List of available International Chemical Reference Substances[1]

International Chemical Reference Substances (ICRS) are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The international pharmacopoeia* or proposed in draft monographs. The ICRS are mainly intended to be used as primary standards to calibrate secondary standards.

Directions for use, and the analytical data required for the use described in the relevant specifications of *The international pharmacopoeia*, are given in the certificates enclosed with the substances when distributed. More detailed analytical reports on the substances may be obtained from the WHO Collaborating Centre for Chemical Reference Substances.

ICRS may also be used in tests and assays not described in *The international pharmacopoeia*. However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed this use.

It is generally recommended that the substances should be stored protected from light and moisture and preferably at a temperature of about 5 °C. When special storage conditions are required, this is stated on the label or in the accompanying leaflet. It is recommended that the user purchase only an amount sufficient for immediate use.

The stability of the ICRS kept at the Collaborating Centre is monitored by regular re-examination, and any material that has deteriorated is replaced by new batches as necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and new yearly lists may be obtained on request.

[1] As updated at the thirty-sixth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 31 May–4 June 1999.

Orders for the ICRS should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier Centrallaboratoriet, ACL
Prismavägen 2
S-141 75 Kungens Kurva
Sweden
Tel.: +46 8 466 1000
Fax: +46 8 740 6040
Email: who.apl@apoteket.se

The ICRS are supplied only in the standard packages indicated in Table 1.

Table 1
Available International Chemical Reference Substances

Reference substance	Package size	Control number
aceclidine salicylate	100 mg	172048
p-acetamidobenzalazine	25 mg	290042
acetazolamide	100 mg	186128
allopurinol	100 mg	287049
amidotrizoic acid	100 mg	196205
2-amino-5-nitrothiazole	25 mg	186131
3-aminopyrazole-4-carboxamide hemisulfate	100 mg	172050
3-amino-2,4,6-triiodobenzoic acid	100 mg	196206
amitriptyline hydrochloride	100 mg	181101
amodiaquine hydrochloride	200 mg	192160
amphotericin B	400 mg	191153
ampicillin (anhydrous)	200 mg	390001
ampicillin sodium	200 mg	388002
ampicillin trihydrate	200 mg	274003
anhydrotetracycline hydrochloride	25 mg	180096
atropine sulfate	100 mg	183111
azathioprine	100 mg	172060
bacitracin zinc	200 mg	192174
beclometasone dipropionate	200 mg	192175
bendazol hydrochloride	100 mg	173066
benzobarbital	100 mg	172051
benzylamine sulfate	100 mg	172052
benzylpenicillin potassium	200 mg	180099
benzylpenicillin sodium	200 mg	280047
bephenium hydroxynaphthoate	100 mg	183112
betamethasone	100 mg	183113
betamethasone sodium phosphate	100 mg	196203
betamethasone valerate	100 mg	190145
betanidine sulfate	100 mg	172053
bupivacaine hydrochloride	100 mg	289054

Table 1 (*continued*)

Reference substance	Package size	Control number
caffeine	100 mg	181102
calcium folinate (leucovorin calcium)	100 mg	194188
captopril	100 mg	197214
captopril disulfide	25 mg	198216
carbamazepine	100 mg	189143
carbenicillin monosodium	200 mg	383043
chloramphenicol	200 mg	486004
chloramphenicol palmitate	1 g	286072
chloramphenicol palmitate (polymorph A)	200 mg	175073
5-chloro-2-methylaminobenzophenone	100 mg	172061
chloroquine sulfate	200 mg	195201
2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg	181106
chlorphenamine hydrogen maleate	100 mg	182109
chlorpromazine hydrochloride	100 mg	178080
chlortalidone	100 mg	183114
chlortetracycline hydrochloride	200 mg	187138
cimetidine	100 mg	190150
ciprofloxacin hydrochloride	400 mg	197210
ciprofloxacin by-compound A	20 mg	198220
ciprofloxacin desfluoro-compound	20 mg	198219
ciprofloxacin ethylenediamine-compound	20 mg	198218
ciprofloxacin fluoroquinolonic acid	20 mg	198217
cisplatin	100 mg	197207
clomifene citrate	100 mg	187136
clomifene citrate *Z*-isomer *see* zuclomifene		
cloxacillin sodium	200 mg	274005
colecalciferol (vitamin D_3)	500 mg	190146
cortisone acetate	100 mg	167006
dapsone	100 mg	183115
desoxycortone acetate	100 mg	167007
dexamethasone	100 mg	388008
dexamethasone acetate	100 mg	288009
dexamethasone phosphoric acid	100 mg	192161
dexamethasone sodium phosphate	100 mg	192158
diazepam	100 mg	172062
diazoxide	100 mg	181103
dicloxacillin sodium	200 mg	174071
dicolinium iodide	100 mg	172055
dicoumarol	100 mg	178077
diethylcarbamazine dihydrogen citrate	100 mg	181100
digitoxin	100 mg	277010
digoxin	100 mg	587011
N,N'-di-(2,3-xylyl)anthranilamide	50 mg	173067
dopamine hydrochloride	100 mg	192159
doxorubicin hydrochloride	100 mg	196202
emetine hydrochloride	100 mg	187134
4-epianhydrotetracycline hydrochloride	25 mg	288097

Table 1 (*continued*)

Reference substance	Package size	Control number
4-epitetracycline hydrochloride	25 mg	293098
ergocalciferol (vitamin D_2)	500 mg	190147
ergometrine hydrogen maleate	50 mg	277012
ergotamine tartrate	50 mg	385013
erythromycin	250 mg	191154
erythromycin B	150 mg	194186
erythromycin C	25 mg	194187
estradiol benzoate	100 mg	167014
estrone	100 mg	279015
etacrynic acid	100 mg	281056
ethambutol hydrochloride	100 mg	179081
ethinylestradiol	100 mg	291016
ethisterone	100 mg	167017
ethosuximide	100 mg	179088
etocarlide	100 mg	172057
flucloxacillin sodium	200 mg	195194
flucytosine	100 mg	184121
fludrocortisone acetate	200 mg	195199
fluorouracil	100 mg	184122
fluphenazine decanoate dihydrochloride	100 mg	182107
fluphenazine enantate dihydrochloride	100 mg	182108
fluphenazine hydrochloride	100 mg	176076
folic acid	100 mg	388019
3-formylrifamycin	200 mg	190149
framycetin sulfate (neomycin B sulfate)	200 mg	193178
furosemide	100 mg	171044
gentamicin sulfate	100 mg	194183
griseofulvin	200 mg	280040
haloperidol	100 mg	172063
hydrochlorothiazide	100 mg	179087
hydrocortisone	100 mg	283020
hydrocortisone acetate	100 mg	280021
hydrocortisone sodium succinate	200 mg	194184
(–)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3-*O*-methylcarbidopa)	25 mg	193180
(–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine (3-*O*-methylmethyldopa)	25 mg	179085
ibuprofen	100 mg	183117
imipramine hydrochloride	100 mg	172064
indometacin	100 mg	178078
o-iodohippuric acid	100 mg	171045
isoniazid	100 mg	185124
kanamycin monosulfate	12 mg	197211
lanatoside C	100 mg	281022
levodopa	100 mg	295065

Table 1 (*continued*)

Reference substance	Package size	Control number
levonorgestrel	200 mg	194182
levothyroxine sodium	100 mg	189144
lidocaine	100 mg	181104
lidocaine hydrochloride	100 mg	181105
liothyronine sodium	50 mg	193179
loperamide hydrochloride	100 mg	194185
mebendazole	200 mg	195195
mefenamic acid	100 mg	173068
melting-point reference substances		
azobenzene (69 °C)	4 g	192168
vanillin (83 °C)	4 g	192169
benzil (96 °C)	4 g	294170
acetanilide (116 °C)	4 g	297171
phenacetin (136 °C)	4 g	297172
benzanilide (165 °C)	4 g	192173
sulfanilamide (166 °C)	4 g	192162
sulfapyridine (193 °C)	4 g	192163
dicyanodiamide (210 °C)	4 g	192164
saccharin (229 °C)	4 g	192165
caffeine (237 °C)	4 g	192166
phenolphthalein (263 °C)	4 g	192167
metazide	100 mg	172058
methaqualone	100 mg	173069
methotrexate	100 mg	194193
methyldopa	100 mg	179084
methyltestosterone	100 mg	167023
meticillin sodium	200 mg	274024
metronidazole	100 mg	183118
nafcillin sodium	200 mg	272025
neamine hydrochloride (neomycin A hydrochloride)	0.5 mg	193177
neomycin B sulfate *see* framycetin sulfate		
neostigmine metilsulfate	100 mg	187135
nicotinamide	100 mg	179090
nicotinic acid	100 mg	179091
nifurtimox	100 mg	194189
niridazole	200 mg	186129
niridazole-chlorethylcarboxamide	25 mg	186130
norethisterone	100 mg	186132
norethisterone acetate	100 mg	185123
nystatin	200 mg	191152
oubain	100 mg	283026
oxacillin sodium	200 mg	382027
oxytetracycline dihydrate	200 mg	189142
oxytetracycline hydrochloride	200 mg	189141
papaverine hydrochloride	100 mg	185127
paracetamol	100 mg	195198

Table 1 (*continued*)

Reference substance	Package size	Control number
paromomycin sulfate	75 mg	195197
pheneticillin potassium	200 mg	167028
phenoxymethylpenicillin	200 mg	179082
phenoxymethylpenicillin calcium	200 mg	179083
phenoxymethylpenicillin potassium	200 mg	176075
phenytoin	100 mg	179089
piperazine adipate	100 mg	197212
piperazine citrate	100 mg	197213
praziquantel	100 mg	194191
prednisolone	100 mg	389029
prednisolone acetate	100 mg	289030
prednisolone hemisuccinate	200 mg	195196
prednisolone sodium phosphate	200 mg	194190
prednisone	100 mg	167031
prednisone acetate	100 mg	169032
probenecid	100 mg	192156
procaine hydrochloride	100 mg	183119
procarbazine hydrochloride	100 mg	184120
progesterone	100 mg	167033
propicillin potassium	200 mg	274034
propranolol hydrochloride	100 mg	187139
propylthiouracil	100 mg	185126
pyrantel embonate (pyrantel pamoate)	500 mg	192157
pyridostigmine bromide	100 mg	182110
reserpine	100 mg	186133
retinol acetate (solution)	5 capsules[a]	898038
riboflavin	250 mg	382035
rifampicin	200 mg	191151
rifampicin quinone	200 mg	190148
sodium amidotrizoate	100 mg	198221
sodium cromoglicate	100 mg	188140
spectinomycin hydrochloride	200 mg	193176
streptomycin sulfate	100 mg	197215
sulfacetamide	100 mg	196200
sulfamethoxazole	100 mg	179092
sulfamethoxypyridazine	100 mg	178079
sulfanilamide	100 mg	179094
sulfasalazine	100 mg	191155
tamoxifen citrate	100 mg	196208
tamoxifen citrate *E*-isomer	10 mg	196209
testosterone enantate	200 mg	194192
testosterone propionate	100 mg	167036
tetracycline hydrochloride	200 mg	180095
thioacetazone	100 mg	171046
4,4′-thiodianiline	50 mg	183116

Table 1 (*continued*)

Reference substance	Package size	Control number
thyroxine sodium *see* levothyroxine sodium		
tolbutamide	100 mg	179086
tolnaftate	100 mg	176074
toluene-2-sulfonamide	100 mg	196204
trimethadione	200 mg	185125
trimethoprim	100 mg	179093
trimethylguanidine sulfate	100 mg	172059
vincristine sulfate	9.7 mg/vial	193181
vitamine A acetate (solution) *see* retinol acetate (solution)		
warfarin	100 mg	168041
zuclomifene	50 mg	187137

[a] Each containing about 8 mg in 230 mg of oil.

WHO Technical Report Series, No. 902, 2002

Annex 2
List of available International Infrared Reference Spectra

International Infrared Reference Spectra are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Full-scale reproductions of spectra produced from authenticated material on a suitable instrument are supplied for use in identification tests described in the specifications for quality control of drugs, published in *The international pharmacopoeia* or proposed in draft monographs.

Precise instructions for the preparation of spectra are given on the label of each reference spectrum. All International Infrared Reference Spectra are distributed together with a document giving further details on the use of such spectra, entitled "General recommendations for the preparation and use of infrared spectra in pharmaceutical analysis".[1]

Orders for International Infrared Reference Spectra should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteket AB
Produktion & Laboratorier Centrallaboratoriet, ACL
Prismavägen 2
S-141 75 Kungens Kurva
Sweden
Tel.: +46 8 466 1000
Fax: +46 8 740 6040
Email: who.apl@apoteket.se

The following International Infrared Reference Spectra are currently available from the Centre:

aceclidine salicylate
acetazolamide
allopurinol
amiloride hydrochloride
amitriptyline hydrochloride
ampicillin trihydrate

[1] *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 4 (WHO Technical Report Series, No. 863).

beclometasone dipropionate
benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride

caffeine (anhydrous)
calcium folinate
carbidopa
chlorphenamine hydrogen maleate
clofazimine
cloxacillin sodium
colchicine
cytarabine

dexamethasone
dexamethasone acetate, monohydrate
dextromethorphan hydrobromide
diazepam
dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride

erythromycin ethylsuccinate
erythromycin stearate
etacrynic acid
ethionamide
ethosuximide

furosemide

gallamine triethiodide
glibenclamide

haloperidol
hydrochlorothiazide

ibuprofen
imipramine hydrochloride
indometacin
isoniazid

lidocaine
lidocaine hydrochloride
lindane

metronidazole
miconazole nitrate

niclosamide
nicotinamide
noscapine

oxamniquine

papaverine hydrochloride
phenobarbital
phenoxymethylpenicillin calcium
phenytoin
primaquine phosphate
propylthiouracil
protionamide
pyrimethamine

salbutamol
salbutamol sulfate
sulfadimidine
sulfadoxine
sulfamethoxazole
sulfamethoxypyridazine

tiabendazole
trihexyphenidyl hydrochloride
trimethoprim

valproic acid
verapamil hydrochloride

WHO Technical Report Series, No. 902, 2002

Annex 3
Good practices for national pharmaceutical control laboratories

General considerations

The government, normally through the drug regulatory authority, establishes and maintains a pharmaceutical control laboratory to carry out the required tests and assays to ensure that active pharmaceutical ingredients, excipients and pharmaceutical products meet quality specifications. Throughout the process of marketing authorization, the laboratory works closely with the national drug regulatory authority. The review of test methods for newly registered drugs plays an important role in ensuring their suitability for the control of quality and safety, and requires a major effort, especially since routine drug testing must also be carried out. Some countries maintain larger establishments called "drug control centres" or "drug control institutes".

The importance of a pharmaceutical control laboratory to a national drug control system has already been outlined in three guidelines on quality assessment (*1–3*).

In most countries the laboratory is responsible for analytical services only, and not for the inspection of pharmaceuticals. However, some aspects of inspection are included in these guidelines.

A governmental pharmaceutical control laboratory provides effective support for a drug regulatory authority acting together with its inspection services. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions to be drawn about the quality of each drug, and also serving as an adequate basis for any subsequent administrative regulations and legal action.

To ensure patient safety, the role of the control laboratory must be defined in the general drug legislation of the country in such a way that the results provided by it can, if necessary, lead to enforcement of the law and legal action.

For the quality of a drug sample to be correctly assessed:

— the submission of a sample to the laboratory, selected in accordance with national requirements, must be accompanied by a statement of the reason why the analysis has been requested;
— the analysis must be correctly planned and meticulously executed;
— the results must be competently evaluated to determine whether the sample complies with the quality specifications or other relevant criteria.

Precise documentation is required to make each operation simple and unambiguous as far as possible (see also Part One, section 2.1).

These guidelines provide advice on the analysis of active pharmaceutical ingredients, excipients and pharmaceutical products. Particular consideration is given to countries with limited resources wishing to establish a governmental pharmaceutical control laboratory, having recently done so, or planning to modernize the existing laboratory.

Many of the recommendations are also relevant to drug quality control testing by the pharmaceutical manufacturer. This is usually a matter of repetitive testing of samples of active pharmaceutical ingredients or of a limited number of pharmaceutical products, whereas, theoretically, governmental control laboratories have to deal with all the drugs on the market and therefore have to use a wider variety of test methods.

Special attention must be given to ensuring the correct and efficient functioning of the laboratory. Planning and future budgets must ensure that the necessary resources are available, inter alia, for the maintenance of the laboratory, as well as for an adequate infrastructure and energy supply. Means and procedures must be in place (in case of anticipated supply problems) to ensure that the laboratory can continue its activities.

The laboratory should be appropriately equipped to respond to all reasonable demands.

Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

active pharmaceutical ingredient
A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient) (*4*).

analytical worksheet
A printed form for recording information about the sample, test procedure and results of testing (see Part Three, section 15).

batch (or lot)
A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch (*4*).

batch number (or lot number)
A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificate of analysis, etc. (*4*).

calibration
The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established (*4*).

calibration of equipment
The documented act of proving that the equipment is performing to predefined tolerances or criteria.

certificate of analysis
Report of the results obtained, including the final conclusion of the examination of a sample issued by the manufacturer and repacker/trader (see Annex 10).

drug
An active pharmaceutical ingredient or a pharmaceutical product (see also pharmaceutical excipient and pharmaceutical product).

good manufacturing practice(s) (GMP)
That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (*4*).

manufacturer
A company that carries out at least one step of manufacture (*4*).

marketing authorization (product licence, registration certificate)
A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the pharmaceutical product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

pharmaceutical excipient
A substance, other than the active pharmaceutical ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system to:

— aid in the processing of the drug delivery system during its manufacture;
— protect, support or enhance stability, bioavailability or patient acceptability;
— assist in pharmaceutical product identification; or
— enhance any other attribute of the overall safety and effectiveness of the drug during its storage or use (*5*, *6*).

pharmaceutical product
Any medicine intended for human or veterinary use, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

qualification of equipment
The act of planning, carrying out and recording the results of the tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated (see Part Two, section 12).

quality assurance
A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use (*4*).

quality control
All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics (*4*).

quality manual
A handbook that describes the various elements of the system for assuring the quality of the test results generated by a laboratory (see Part One, section 2.1).

quality specification
Explicit written test procedures and requirements that must be met.

quality system
An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or services)

will satisfy given requirements for quality (see Part One, sections 2.1 and 3.1).

specification
A document describing in detail the requirements with which the pharmaceutical products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

specifications archive
An up-to-date collection of all quality specifications and related documents (see Part Two, section 9).

standard operating procedure (SOP)
An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation (*4*).

test report
The report of the results, including the final conclusion of the analysis of a sample which has been submitted by a laboratory in another country or in the field not having appropriate facilities to perform certain tests, and issued by the official pharmaceutical control laboratory that performed the test. This is often in the same style as a certificate of analysis (see Part Three, section 17.3).

traceability
Traceability aims at ensuring that the results of laboratory measurements using procedures of lower metrological order are reproducible and scientifically acceptable by referring to an internationally agreed denominator by means of a reference procedure of highest metrological order and/or a primary reference material (see Part Two, section 13).

validation of analytical procedures/methods
The documented evidence that analytical procedures or methods are suitable for their intended purpose (*7*).

verification of methods
Verification is conducted where the methods are compendial to confirm whether the pharmaceutical product as compounded can be analysed satisfactorily by the official method.

Part One. Management and infrastructure

1. Organization and management

1.1 The laboratory, or the organization of which it is part, must be an entity that is legally authorized to function and can be held legally responsible.

1.2 The laboratory must be organized and operate so as to meet the requirements laid down in these guidelines.

1.3 The laboratory must:

(a) have managerial and technical personnel with the authority and resources needed to carry out their duties and to identify the occurrence of departures from the quality system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;

(b) have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may adversely affect the quality of their work;

(c) define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization, such as the ministry or the drug regulatory authority, and the relationships between management, technical operations, support services and the quality system;

(d) specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work which affects the quality of the tests and/or calibrations, validations and verifications;

(e) provide adequate supervision of staff, including trainees, by persons familiar with the test and/or calibration, validation and verification methods and procedures, as well as their purpose and the assessment of the results;

(f) have a technical manager who has overall responsibility for the technical operations and the provision of resources needed to ensure the required quality of laboratory operations; and

(g) have appropriate safety procedures (see Part Four).

1.4 The laboratory, regardless of whether it is small (without subunits) or large (and possibly divided into subunits), must have a central registry with the following functions:

(a) receiving, distributing and supervising the consignment of the samples to the specific units;

(b) keeping records on all incoming samples and accompanying documents;

(c) ensuring the precise allocation of responsibilities, particularly in the designation of specific units for particular types of drugs; and

(d) maintaining a specifications archive (see Part Two, section 9) containing an up-to-date collection of all quality specifications and related documents.

1.5 In a large laboratory, communication and coordination must be guaranteed between the staff involved in the testing of the same sample in different units.

2. Quality system

2.1 The laboratory management establishes, implements and maintains a quality system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes. The laboratory management must describe its policies, systems, programmes, procedures and instructions to the extent necessary to enable the laboratory to assure the quality of the test results that it generates. The documentation used in this quality system must be communicated and available to, and understood and implemented by, the appropriate personnel. The elements of this system must be documented in a quality manual, available to the laboratory personnel, which must be maintained and updated by a nominated responsible member of the laboratory personnel. The quality manual must contain as a minimum:

(a) the structure of the laboratory (organizational chart);

(b) the operational and functional activities pertaining to quality, so that each person concerned will know the extent and the limits of his or her responsibilities;

(c) the general internal quality assurance procedures;

(d) references to specific quality assurance procedures for each test;

(e) information on participation in appropriate proficiency testing schemes, use of reference materials, etc.;

(f) details of satisfactory arrangements for feedback and corrective action when testing discrepancies are detected;

(g) a procedure for dealing with complaints;

(h) a flow-chart for samples;

(i) details of audit and quality system review;

(j) information on the appropriate qualifications that personnel are required to possess;

(k) information on initial and in-service training of staff;

(l) a quality policy statement, including at least the following:

  (i) a statement of the laboratory management's intentions with respect to the standard of service it will provide;

  (ii) the purpose of the quality system;

  (iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification, as a service to its clients;

  (iv) the laboratory management's commitment to compliance with the content of these guidelines;

  (v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work.

2.2 The quality system must be reviewed systematically and periodically (internal and external audits) by, or on behalf of, the management to ensure the continued effectiveness of the arrangements and apply any necessary corrective measures. Such reviews must be recorded, together with details of any corrective action taken.

2.3 The laboratory management must appoint a member of the staff as quality manager, who, irrespective of other duties and responsibilities, should have defined responsibilities and authority for ensuring that the quality system is implemented and followed at all times. The quality manager must have direct access to the highest level of management at which decisions are taken on laboratory policies or resources.

3. Control of documentation

3.1 Documentation is an essential part of the quality system. The laboratory must establish and maintain procedures to control and review all documents (both internally generated and from external sources) that form part of the quality documentation.

4. Records

4.1 The laboratory must establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance and disposal of, and access to, all quality documentation and technical records.

4.2 All original observations, calculations and derived data, calibration, validation and verification records, etc., and final results must be retained on record for an appropriate period of time in accordance with national regulations. Ideally, they should be kept for the whole length of time that the drug concerned is on the market. The records for each test must contain sufficient information to permit the tests to be repeated. The records must include the identity of the personnel involved in the sampling, preparation and testing of the samples. The records of samples to be used in legal proceedings should be kept according to the legal requirements applicable to them.

4.3 All records must be legible, readily retrievable, stored and retained, using facilities that provide a suitable environment that will prevent modification, damage or deterioration and/or loss. The conditions under which all original records are stored must be such as to ensure their security and confidentiality. Quality records must include reports from internal (and external, if performed) audits and management reviews, including records of possible corrective and preventive actions.

4.4 Authorized written standardized operating procedures (SOPs) are required, including, but not limited to, instructions for administrative and technical operations, such as:

(a) the purchase and receipt of consignments of materials (e.g. samples, reference materials, reagents);

(b) the internal labelling, quarantine and storage of materials;

(c) the appropriate installation of each instrument and item of equipment;

(d) sampling and inspection;

(e) the testing of materials, with descriptions of the methods and equipment used;

(f) the qualification of equipment;

(g) the calibration of analytical apparatus;

(h) maintenance, cleaning and sanitation;

(i) safety measures;

(j) actions relating to personnel matters, including qualifications, training, clothing and hygiene;

(k) environmental monitoring;

(l) the preparation and control of reference materials.

5. Data-processing equipment

5.1 For computers, automated tests or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, the laboratory must ensure that:

(a) calculations and data transfers are systematically subject to appropriate verifications;

(b) computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being adequate for use;

(c) procedures are established and implemented for protecting the integrity of data. Such procedures must include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection, and the storage, transmission and processing of data;

(d) computers and automated equipment are maintained so as to function properly, and are provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data;

(e) procedures are established and implemented for making, documenting and controlling for changes to information maintained in computerized systems; and

(f) procedures exist to protect and keep back-up data on computers or other means (e.g. magnetic tapes, diskettes and CD-ROMs) at all times, and to prevent unauthorized access or amendments to the data.

6. Personnel

6.1 The laboratory must have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions. They should be free from any conflict of interest and not subject to any pressure that would interfere with the quality of the results.

6.2 The laboratory management must ensure the competence of all persons operating specific equipment, instruments or other devices,

who are performing tests and/or calibrations, validations or verifications. Their duties also involve the evaluation of results as well as signing test reports (see Appendix 1) and calibration certificates.

6.3 Staff undergoing training must be appropriately supervised, and a formal assessment after training is recommended. Personnel performing specific tasks must be appropriately qualified in terms of their education, training, experience and/or demonstrated skills, as required.

6.4 The laboratory personnel must be permanently employed or under contract. The laboratory must ensure that additional technical and key support personnel who are under contract are supervised and sufficiently competent and motivated, and that their work is in accordance with the good practice of the laboratory.

6.5 The laboratory must maintain current job descriptions for managerial, technical and key support personnel involved in tests and/or calibrations, validations and verifications. The laboratory must also maintain records of all technical personnel, including those under contract, describing their areas of competence, educational and professional qualifications, training, skills and experience. This information must be readily available and must include the date on which authorization and/or competence was confirmed. The criteria on which the authorization is based must also be given, together with the name of the confirming authority.

6.6 The laboratory must have the following managerial and technical personnel:

(a) a head of laboratory (supervisor), who must be of high professional standing with extensive experience in drug analysis and laboratory management in a pharmaceutical control laboratory in the regulatory sector or in industry. The head of laboratory also takes final responsibility for recommending any regulatory action in the event of non-compliance of a tested sample. The person's function is to ensure that:

    (i) all key members of the laboratory staff have the requisite competence and are given grades matching their responsibilities;

    (ii) standard samples are analysed periodically;

    (iii) the adequacy of existing staffing, management and training procedures is reviewed periodically;

    (iv) "self-checking" procedures for instrument operators are devised;

(v) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged;

(vi) the safe keeping of any narcotics (see Part One, sections 7.10–7.12) kept in the workplace is under the supervision of an authorized person;

(b) a head of central registry, who must have wide experience in drug analysis and be responsible for:

(i) receiving and keeping records of all incoming samples and accompanying documents;

(ii) supervising their consignment to the specific units concerned;

(iii) monitoring the progress of analyses and the dispatch of completed reports (see also Part One, section 1.4);

(iv) if required, collating and evaluating the test results for each analysis;

(c) analysts, who must be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by management and to supervise technical staff;

(d) technical staff, who should hold diplomas in their subjects awarded by technical or vocational schools;

(e) a storekeeper (see Part Two, section 10.13), who is responsible for keeping the central store and must have appropriate competence and be trained to handle reagents and materials with the necessary care and safety;

(f) a quality manager (see Part One, section 2.3).

6.7 In large laboratories with subunits, the following additional personnel are necessary:

(a) heads of various subunits;

(b) a reference material coordinator (see Part Two, section 11.8).

6.8 The more routine analyses performed, the greater the proportion of technicians required. Non-routine work, and particularly the review of test methods for newly registered drugs, requires a higher proportion of fully qualified specialists. In general, the ratio of technicians to analysts in a routine testing environment has been shown to be 3:1 in a chemical or physicochemical unit, and 5:2 in a biological or microbiological laboratory.

7. Premises

7.1 The laboratory should be of a suitable size, construction and location. Safety requirements should be taken into consideration in the design (see Part Four).

7.2 The design of the laboratory should be such as to provide an adequate degree of separation of any activity which may interfere with the proper conduct of each study.

7.3 The laboratory should have a sufficient number of rooms or areas to ensure that test systems are isolated from one another.

7.4 The premises must have suitable testing and safety equipment. The necessary energy sources should be available; if the line voltage is variable, suitable voltage stabilizers should be installed.

7.5 Storage rooms or areas should be available, as needed, for supplies and materials, and should be conveniently located. These rooms should be separated from those areas housing the test systems and should provide adequate protection against infestation, contamination and/or deterioration.

7.6 To prevent contamination or mix-ups, separate rooms or areas for the receipt and storage of test and reference items should be available, as well as for the mixing of test items with a vehicle.

7.7 Storage rooms or areas for test items should be separate from those containing the test systems. They should be constructed in such a way as to preserve the identity, concentration, purity and stability of the test item, and ensure safe storage of hazardous substances. All storage areas must be located and equipped in accordance with fire regulations. For safety reasons, and to reduce contamination of the laboratory environment, flammable reagents, fuming and concentrated acids and bases, volatile amines, etc., must never be kept in the laboratory without good reason.

Central store

7.8 Separate central storage facilities must be maintained for the secure storage of samples, retained samples (see Part Three, section 18), and reagents, laboratory accessories (see Part Two, sections 10.12–10.14) and reference materials (see Part Two, section 11). Storage facilities must be equipped to store material, if necessary, under refrigeration and securely locked. Access must be restricted to designated personnel.

7.9 The central store should be organized in such a way so as to accommodate incoming and outgoing samples, reagents, equipment, instruments and other devices.

7.10 Appropriate safety regulations must be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used.

7.11 Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances must be clearly marked as "Poison". They must be kept separately from other reagents in locked cabinets.

7.12 The designated responsible member of staff must maintain a register of these substances. The head of each unit must accept personal responsibility for the safe keeping of any of these reagents kept in the workplace (see Part One, section 6.6).

7.13 Archive facilities should be provided to ensure the secure storage and retrieval of all documents (internally generated or from external sources), samples of test items and specimens. The design and condition of the archives should be such as to protect the contents from untimely deterioration. Access to the archives must be restricted to designated personnel.

7.14 The handling and disposal of wastes should be carried out in such a way as not to jeopardize the integrity of studies and the environment. Appropriate facilities for the collection, storage and disposal of wastes should be available, as well as a means of decontamination, where applicable, and transportation.

7.15 The environment in which the tests are undertaken must not be such as to invalidate the test results or adversely affect the required accuracy of measurements. This applies particularly to sites other than permanent laboratory premises. Testing premises must be protected, as required, from conditions such as heat, cold, dust, moisture, steam, noise, vibration and electromagnetic disturbance or interference. Devices to monitor the environmental conditions must be installed, if required by the nature of the testing. Access to, and use of, all test areas must be controlled and limited to the minimum necessary for their designated purpose. Persons external to the laboratory must satisfy the specified conditions of entry. Adequate measures must be taken to ensure good housekeeping in the test laboratory.

8. Equipment, instruments and other devices

8.1 Equipment, instruments and other devices must be designed, constructed, adapted, located, calibrated, qualified, verified and maintained as required by the operations to be carried out in the local environment. The user should purchase the equipment from an agent capable of providing full technical support and maintenance

when necessary. Documentation should be written in the language employed in the laboratory.

8.2 To ensure proper sampling and measurement, the laboratory must have the required test equipment, instruments and other devices for the correct performance of the tests and/or calibrations, validations and verifications (including the preparation of test and/or calibration items, and the processing and analysis of test and/or calibration data). As a guide, a list of basic equipment, instruments and other devices is given in Appendix 2.

8.3 Equipment, instruments and other devices, including those used for sampling, must meet the laboratory's requirements, and comply with the relevant standard specifications, as well as be verified and/or calibrated (see Part Two, section 12).

Part Two. Materials and setting-up of equipment, instruments and other devices

9. Specifications archive

9.1 It is recommended that every pharmaceutical control laboratory should have a specifications archive. Current versions of all necessary specifications should be kept in accordance with the national legislation, as described in pharmacopoeial compendia or in manufacturers' registration documents. All updates and corrections must be noted in the principal volumes of pharmacopoeias to prevent the use of obsolete sections. Additional or replacement pages for loose-leaf publications must be inserted immediately upon receipt, and pages no longer valid must be removed. Adequate numbers of supplements and addenda must be available.

Content

9.2 The specifications archive must contain:

(a) a list of all the pharmacopoeias in the laboratory;

(b) a file of non-pharmacopoeial quality specifications for drugs tested to specifications established either by the manufacturer or by the laboratory itself and approved by the authority responsible for drug control. In this file, each entry must be numbered and dated so that the latest version can easily be recognized. In addition, the version in the archive file (master copy) must bear the date of approval by the national registration authority or the specific unit and contain any other information relevant to the status of the quality specifications. All subsequent corrections or

changes must be entered in the master copy and endorsed with the name and signature of the person responsible and the date. A revised document should be produced as soon as possible.

9.3 Master copies of documents should not be released from the archive; photocopies must be accounted for and controlled for laboratory use.

9.4 Manufacturers' specifications are the property of the company concerned. They are often made available to governments strictly for the purpose of assessing applications for marketing authorization. The pharmaceutical control laboratory may need to negotiate their release with manufacturers or even, in some cases, to develop independent specifications. National laboratories may be asked routinely to give their opinion on the specifications for each newly introduced pharmaceutical product before it is authorized for marketing by the drug regulatory authority.

9.5 In a large laboratory the specifications archive supervisor will provide a documentation service and will be responsible for:

(a) updating all pharmacopoeias, including the insertion of supplements, addenda and descriptions of corrective measures used in the laboratory;

(b) maintaining a specifications file for all drugs authorized for marketing within the country concerned.

10. Reagents

10.1 All reagents and chemicals, including solvents and materials used in tests and assays, must be of appropriate quality.

10.2 Reagents must be purchased from reputable manufacturers or dealers, and be accompanied by the certificate of analysis. In some cases, a list of pre-qualified suppliers will have to be established.

10.3 In the preparation of reagents in the laboratory:

(a) responsibility for this task must be clearly specified in the job description of the person assigned to carry it out;

(b) prescribed procedures must be used which are in accordance with published pharmacopoeial or other standards, where available. Records should be kept of the preparation and standardization of volumetric solutions.

10.4 The labels of all reagents must clearly specify:

(a) the contents, the manufacturer, the date received and, as appropriate, the concentration, standardization factor, shelf-life and

storage conditions. Labels for reagents prepared in the laboratory must state the date of preparation, and give the name and initials of the responsible technician;

(b) for volumetric solutions prepared by dilution, the name of the manufacturer of the original reagent, the date of preparation, the date of standardization, the dilution factor, and the name of the responsible technician.

10.5 In the transportation and subdivision of reagents:

(a) they must not be moved unnecessarily from unit to unit;

(b) whenever possible, they must be transported in the original containers;

(c) when subdivision is necessary, scrupulously clean, fully labelled containers must always be used.

Inspection

10.6 All reagent containers must be inspected to ensure that the seals are intact both when they are delivered to the central store and when they are distributed to the units.

10.7 These inspections must be recorded on the label, together with the date, and the name and initials of the person responsible.

10.8 Reagents appearing to have been tampered with should be rejected; however, this requirement may exceptionally be waived if the identity and purity of the reagent concerned can be confirmed by testing.

Distilled water and deionized water

10.9 Water should be considered as a reagent.

10.10 Precautions must be taken to avoid contamination during its supply, storage and distribution.

10.11 Stocks must be verified regularly to ensure that pharmacopoeial and other official quality requirements are met.

Storage

10.12 Stocks of reagents must be maintained in a central store under the appropriate storage conditions. The store must contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers. Special equipment may be needed for the transfer of larger volumes of corrosive liquids.

10.13 The storekeeper is responsible for looking after the central store and its inventory, and for noting the expiry date of chemicals and reagents. Training may be needed in handling chemicals with the necessary care and safety.

10.14 The laboratory must provide separate rooms or areas for storing flammable substances, fuming and concentrated acids and bases, volatile amines and other reagents, such as hydrochloric acid, nitric acid, ammonia and bromine. Self-igniting materials, such as metallic sodium and potassium, must also be stored separately.

11. Reference materials

11.1 Reference materials (*8*, *9*) (e.g. official reference substances and reference preparations, secondary reference materials and non-official materials prepared in the laboratory as working standards) are necessary for the testing and/or calibration, validation or verification of a sample or of equipment, instruments or other devices.

Registration and labelling

11.2 An identification number must be assigned to all reference materials, whether newly delivered or prepared in the laboratory.

11.3 A new identification number must be assigned to each new batch.

11.4 This number must be marked on each vial of the material.

11.5 The identification number must be quoted on the analytical worksheet every time the material is used (see Part Three, section 15.5).

Central register

11.6 Details concerning all reference materials required are compiled in a central register, which may be a record book, a card file, or data-processing equipment.

11.7 The central register must provide the following information:

(a) the identification number of the material;

(b) a precise description of the material;

(c) the source;

(d) the date of receipt;

(e) the batch designation or other identification code;

(f) the intended use of the material (e.g. as an infrared reference material, as an impurity reference material for thin-layer chromatography, etc.);

(g) the location of storage in the laboratory, and any special storage conditions;

(h) any further necessary information (e.g. the results of inspections).

11.8 The functions of a person serving as a reference material coordinator in a large laboratory (see Part One, section 6.7) must be specified. This person is responsible for keeping the central register for reference materials.

11.9 If a national drug laboratory is required to establish reference materials for use by other institutions or by drug manufacturers, a separate reference materials unit, which would perform all the duties of the reference material coordinator, may be required.

Information file

11.10 In addition to the central register, a file must be kept in which all information on the properties of each reference material is entered.

11.11 For working standards prepared in the laboratory, the file must include the results of all tests and verifications used to establish the standard; these must be initialled by the responsible analyst.

Inspection

11.12 All reference materials must be inspected at regular intervals to ensure that deterioration has not occurred and that the storage conditions are appropriate for the materials concerned.

11.13 The results of these inspections must be recorded in the central register and/or the information file, and initialled by the responsible analyst.

11.14 Further details on the handling and storage of reference materials are given in the general guidelines on the establishment, maintenance and distribution of reference materials (*8*). A compilation of national, regional and international reference substances, which is kept up to date, is available from the Secretariat (*9*).

12. Calibration, validation and verification of equipment, instruments and other devices

12.1 All equipment, instruments and other devices used to measure the physical properties of substances must be regularly calibrated, validated and verified.

12.2 Specific procedures must be established for each type of equipment, instrument and other device, having regard to the extent to which they are used, verified and calibrated at regular intervals according to the SOP.

For example:

(a) pH meters are verified with standard certified buffer solutions at least once a day;

(b) infrared spectrophotometers require verification at least once a day and calibration at regular intervals.

12.3 Only authorized personnel should operate equipment, instruments and devices. Up-to-date instructions on the use, maintenance, verification and calibration of equipment, instruments and devices (including any relevant manuals provided by the manufacturer) must be readily available for use by the appropriate laboratory personnel (e.g. a copy of these instructions should be placed beside each apparatus, together with a schedule of the dates on which it is due for verification and/or calibration). The results of the verification must be recorded on a control chart, forming the basis for the timing of calibration.

12.4 Each item of equipment, instrument or other device used for testing, verification and calibration must, when practicable, be uniquely identified.

12.5 Records must be kept of each item of equipment, instrument or other device used to perform testing, verification and/or calibration. The records must include at least the following:

(a) the identity of the equipment, instrument or other device;

(b) the manufacturer's name, the type identification, serial number or other unique identification;

(c) the verification and/or calibration required to comply with the specifications;

(d) the current location, where appropriate;

(e) the manufacturer's instructions, if available, or an indication of their location;

(f) the dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria, and the due date of the next verification and/or calibration;

(g) the maintenance carried out to date and the maintenance plan;

(h) a history of any damage, malfunction, modification or repair.

It is also recommended that records should be kept and additional observations made of the time for which the equipment, instruments or devices were used.

12.6 To prevent contamination or deterioration, the laboratory must perform systematic verifications, specify procedures and have an established plan for the safe handling, transport, storage, use and maintenance of measuring equipment so as to ensure that it functions properly.

12.7 Maintenance procedures must be established (regular servicing must be performed by a team of maintenance specialists, whether internal or external, whenever possible).

12.8 Equipment, instruments and other devices, either subjected to overloading or mishandling, giving suspect results, shown to be defective or outside specified limits, must be taken out of service and clearly labelled or marked. Wherever possible, they must not be used until they have been repaired and shown by calibration or testing to perform correctly.

12.9 All equipment, instruments and other devices under the control of the laboratory and requiring calibration must be labelled, coded or otherwise identified to indicate the status of calibration and the date when recalibration is due.

12.10 When the equipment, instruments and other devices are outside the direct control of the laboratory for a certain period of time, the laboratory must ensure that their function and calibration status are verified and shown to be satisfactory before they are returned to service.

12.11 Depending on the types of analytical equipment, instruments and other devices used, their fragility, the extent to which they are used, and the skills required to operate them, they can be:

(a) grouped together;

(b) dispersed between the various units;

(c) protected from extreme states of humidity or temperature in a specially designed area;

(d) adequately protected so as to be resistant to corrosion;

(e) protected against mould and fungal growth.

12.12 Further guidance:

(a) Procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures, and

potentiometers for pH determinations are given in *The international pharmacopoeia* (*10*), together with methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers.

(b) Guidelines for the validation of analytical procedures used in the examination of chemical and physicochemical attributes of pharmaceutical materials are provided in Annex 5 of the thirty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (*11*). Other guidelines are also available (*12*).

13. Traceability

13.1 Traceability aims at ensuring that the results of laboratory measurements using procedures of lower metrological order are reproducible and scientifically acceptable by referring to an internationally agreed denominator by means of a reference procedure of highest metrological order and/or a primary reference material. The analytical specificities of each measurement procedure and reference material that is used to ascertain traceability must therefore be known. A transfer protocol, together with a detailed description of the traceability chain, including measurement procedures and reference materials at all levels, must be prepared. The protocol must be meticulously followed to ensure the reproducibility of results.

13.2 Traceability takes into account the fact that the validity of laboratory investigations is limited by uncertainties. It applies to measurement procedures as well as to reference materials used for the calibration of such procedures.

13.3 For the majority of quantities, a variety of measurement procedures have been developed to meet the requirements of the intended purpose of analysis.

13.4 Both quantitative and qualitative measurement procedures are available (*8*).

13.5 Quantitative measurement procedures provide numerical results that vary in terms of their precision, accuracy, and the analytical sensitivity and selectivity of measurement. A hierarchy of procedures can be established on the basis of the accuracy of measurement, as follows:

(a) Measurement procedures of the highest metrological order (primary reference measurement procedures). These are used to quantitatively measure a quantity of known physicochemical structure with a negligible measurement error (bias). The result obtained by the use of such a procedure, which some experts

refer to as a definitive method, is nearest to the "true value". (Examples include weighing, gas chromatography–mass spectrometry and isotope dilution techniques.)

(b) Reference measurement procedures (secondary reference measurement procedures). The accuracy of such procedures is assessed by:

  (i) comparing the results of measurement by such a procedure with those of a measurement procedure of highest metrological order;

  (ii) calibration with an international reference material with an assigned value in arbitrary units;

  (iii) calibration with a primary reference material (e.g. an International Chemical Reference Substance). (Examples include flame photometry, atomic absorption spectroscopy and assay methods.)

(c) A routine measurement procedure (selected measurement procedure). This measures with sufficient reliability and practicality for its intended purpose. The extent of any systematic deviation of the results from their true value, as determined by a routine measurement method, should be known.

13.6 "Semi-quantitative" measurement procedures provide results that are less accurate and less precise than those obtained by quantitative measurement. Such procedures measure a quantity in discrete concentration intervals. In pharmacopoeias, these tests are referred to as "limit tests"; they compare the response of the test substance with that of the reference substance at the limiting level. The intervals are expressed as rough estimates on an ordinal scale. In laboratory observations made after geometrical dilution of the specimen, the results are expressed in terms of titres. Typically, no linear relation exists between the signal of observation and the concentration of the quantity.

13.7 Qualitative measurement procedures are descriptive, and may distinguish between the absence and presence of a quantity in samples. The results are expressed in terms of a nominal scale. The distinction between the presence and absence of the quantity in a sample is related to the ability of the measurement procedure to detect that quantity at a minimal concentration. The minimal concentration of a quantity that will be positively indicated by the test system (limit of detection), or the ability to quantify the analyte in the presence of other components of the specimen (limit of quantification), may vary from one test system to another. A different approach is

used for pharmacopoeial standards and for substances that are established and distributed by pharmacopoeial authorities, which give the information provided by certificates of analysis together with expiry dates.

13.8 Reference materials are used for the calibration of measurement procedures, and have assigned values of a quantity. These values should be established, whenever possible, by means of a method of highest metrological order. The assigned values may also be established by means of more than one measurement procedure, provided that the results are not significantly different. A hierarchy of reference materials also exists, as follows:

(a) A designated primary chemical substance is one that is widely acknowledged to possess the appropriate qualities within a specified context, and whose value is accepted without comparison with another chemical substance being required (*8*).

(b) A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance. The extent of characterization and testing of a secondary chemical reference substance may be less than that required for a primary chemical reference substance. This definition may apply, inter alia, to working standards (see below).

(c) International biological standards are biological reference materials which have been exhaustively studied and which meet international requirements for accuracy, consistency and stability. They are established by the WHO Expert Committee on Biological Standardization. Such standards are generally assigned potency values expressed in terms of International Units (IU) of biological activity, on the basis of an extensive international collaborative study.

(d) A working standard (working calibrator) has an assigned value of a quantity using one or more selected measurement procedures. This calibrator is sometimes called a "manufacturer's master calibrator" or an "in-house calibrator". The working standard should be compatible with the manufacturer's selected measurement procedure and with the procedure to be calibrated.

(e) A manufacturer's product calibrator is used for the calibration of a routine measurement procedure of an end user.

(f) A control material is used for testing the precision and accuracy of the results. Such a material should have a matrix similar to that

of the samples to be measured. Assigned values, together with the uncertainty of measurement appropriate to the intended use, should be given.

Part Three. Working procedures

14. Incoming samples

14.1 Guidelines on sampling procedures for industrially manufactured pharmaceuticals were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-first meeting (*13*). A compendium of guidelines is also available (*14*).

14.2 Samples received by the laboratory may be routine samples for control, samples suspected of not complying with the specifications, or samples submitted in connection with a marketing authorization process. Close collaboration with those providing the samples is important. In particular, pharmaceutical inspectors who frequently submit samples should note that the sample must be large enough to enable, if required, a number of replicate tests to be carried out (see Part Three, section 16.3) and for part of the sample to be retained (see Part Three, section 18).

14.3 It is common for three samples to be taken; these must be sealed and documented. Where non-compliance is suspected, two samples are retained in the laboratory and the third is retained by the manufacturer. The first sample is tested in accordance with the specification. If it is non-compliant and the manufacturer objects to the results, the third sample is analysed in the presence of the manufacturer's specialist. The second sample is analysed in case of dispute.

14.4 The laboratory must have a sampling plan and an internal procedure for sampling, available to all analysts and technicians within the laboratory.

Test request

14.5 A standard test request form must be filled out during sampling and must accompany each sample submitted to the laboratory.

14.6 The test request form must provide or leave space for the following information:

(a) the name of the institution or inspector that supplied the sample;

(b) the source of the material;

(c) a full description of the drug, including its composition, International Nonproprietary Name (INN) (if available), brand name(s),

dosage form and concentration or strength, the manufacturer, the batch number (if available) and the marketing authorization number;

(d) the size of the sample;

(e) the reason for requesting the analysis;

(f) the date on which the sample was collected;

(g) the size of the consignment from which it was taken, when appropriate;

(h) the expiry date (for pharmaceutical products) or the retest date (for starting materials or pharmaceutical excipients);

(i) the pharmacopoeial specifications or other official specifications to be used for testing;

(j) a record of any further comments (e.g. discrepancies found);

(k) the required storage conditions.

Registration and labelling

14.7 All newly delivered samples and the accompanying documents (e.g. the test request) must be assigned a registration number. Separate registration numbers must be assigned to requests referring to two or more drugs, different dosage forms, or different batches of the same drug. If applicable (see Part Three, section 18), a registration number must also be assigned to any incoming retained sample.

14.8 A label bearing the registration number must be affixed to each container of the sample. Care must be taken to avoid obliterating any other markings or inscriptions.

Central register

14.9 A central register must be kept, which may be a record book, a card file, or data-processing equipment, where the following information is recorded:

(a) the registration number of the sample;

(b) the date of receipt;

(c) the specific unit to which the sample was forwarded.

Inspection of the submitted sample

14.10 The sample received must immediately be inspected by laboratory staff to ensure that the labelling is in conformity with the information contained in the test request. The findings must be recorded,

dated and initialled. If discrepancies are found, or if the sample is obviously damaged, the fact must be recorded without delay on the test request form. Any queries must be immediately referred back to the provider of the sample.

Storage

14.11 The sample prior to testing (see Part Three, section 16.1), the retained sample (see Part Three, section 18) and any portions of the sample remaining after performance of all the required tests must be stored safely taking into account, if necessary, the storage conditions (*15, 16*) specified for the sample.

Forwarding to testing

14.12 The specific unit to which the sample is sent to for testing is determined by the head of central registry.

14.13 The examination of a sample must not be started before the relevant test request has been received.

14.14 The sample must be properly stored until all relevant documentation has been received.

14.15 A request for analysis may be accepted verbally only in case of emergencies. All details must immediately be placed on record, pending the receipt of written confirmation.

14.16 Data must be recorded on the analytical worksheet (see Part Three, section 15).

14.17 Copies or duplicates of all documentation must accompany each numbered sample when sent to the specific unit.

14.18 Testing must be performed as described under Part Three, section 16.

15. Analytical worksheet

15.1 The analytical worksheet is an internal document in printed form for recording information about the sample, the test procedure and the results of testing. It may be complemented by the raw data obtained in the analysis.

Purpose

15.2 The analytical worksheet contains:

(a) confirmation that the sample being examined is in accordance with the requirements;

(b) documentary evidence to support regulatory action, if necessary.

Use

15.3 A separate analytical worksheet must be used for each numbered sample.

15.4 If necessary, a further set of analytical worksheets in duplicate can be used for a collaborating unit (after testing, all the results should be assembled in a single analytical worksheet, using the data from all collaborating units).

Content

15.5 The analytical worksheet must provide or leave space for the following information:

(a) the registration number of the sample (see Part Three, section 14.7);

(b) page numbering, including the total number of pages (including annexes);

(c) the date of the test request;

(d) the date on which the analysis was performed;

(e) the name and signature of the analyst;

(f) a description of the sample received;

(g) references to the specifications to which the sample was tested, including the limits (adding any special methods employed) (see Part Three, section 14.6), and the reference number of the specifications, if available (e.g. pharmacopoeial monograph);

(h) the results obtained with the tested sample (see Part Three, section 16.4);

(i) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), signed by each of the analysts involved and initialled by the supervisor;

(j) the identity of the test equipment used (see Part Two, section 12);

(k) any further comments, for example, for internal information (see Part Three, section 16.1). The above information may be complemented by:

    (i) detailed notes on the specifications selected and the methods of assessment used (see Part Three, section 15.7);

    (ii) whether and when portions of the sample were forwarded to other units for special tests (for example, mass spectrometry,

X-ray diffraction), and the date when the results were received;

(iii) the identification number of any reference material (see Part Two, section 11.5);

(iv) if applicable, the results of an instrument verification;

(v) if applicable, the results of a reagent verification.

15.6 The completed analytical worksheet must be signed by the responsible analyst(s) and initialled by the supervisor.

Selection of the specifications to be used

15.7 The specifications necessary to assess the sample may be those given in the test request; these are usually an existing particular pharmacopoeial monograph, or the manufacturer's specifications. If no precise instruction is given, the specifications in the officially recognized national pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other nationally recognized specifications. If no suitable method is available:

(a) the specifications contained in the product licence may be requested from the manufacturer and validated, if the general policy of the laboratory permits this action (see Part Two, section 9.4); or

(b) the requirements are drafted in the laboratory itself on the basis of published information and any other relevant documentation and should be validated by the testing laboratory before they are adopted as a SOP (*1–3*).

15.8 For official specifications, the current version must be available (see Part Two, section 9.1).

Filing

15.9 The analytical worksheet must be placed on file for safe keeping, together with any attachments, including calculations and tracings of instrumental analyses.

15.10 If the analytical worksheet is stored in a central archive, a copy should be retained in the specific unit concerned for easy reference.

15.11 The analytical test report (see Part Three, sections 17.3 and 17.4) must be prepared on the basis of the worksheet (see Appendix 1 and Annex 10).

15.12 When mistakes are made in analytical worksheets or when data or text need to be amended, the old information should be deleted by

means of a single line (not erased nor made illegible) and the new information added alongside. All such alterations should be initialled or signed by the person making the correction and the date of the change inserted. The reason for the change should also be given on the worksheet.

16. Testing

16.1 The sample must be tested in accordance with the workplan of the laboratory after completion of the preliminary procedures. If this is not feasible, the reasons must be noted, for example in the analytical worksheet (see Part Three, section 15), and the sample must be stored in a special place which is kept locked (see Part Three, section 14.11).

16.2 Specific tests required, such as mass spectrometry or X-ray diffraction, may need to be carried out by another unit or by a specialized external laboratory. The responsible person should prepare the request and arrange for the transfer of the required number of units (bottles, vials, tablets) from the sample. Each of these units must bear the correct registration number.

Guidance for performing test methods

16.3 Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned. Where system suitability criteria are defined in the method, they should be fulfilled.

16.4 All values obtained from each test, including blank results, must immediately be entered on the analytical worksheet, and all graphical data, whether obtained from recording instruments or plotted by hand, must be attached (see Part Three, section 15).

17. Evaluation of test results

17.1 Test results must be reviewed and, where appropriate, evaluated statistically after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications used. The evaluation should take into consideration the results of all the tests. Whenever doubtful results are obtained, they should be investigated. The complete testing procedure needs to be checked according to the internal quality system (see also Part One, section 2). Doubtful results can be rejected only if they are clearly due to error, which has been identified.

17.2 All conclusions must be entered on the analytical worksheet (see Part Three, section 15) by the analyst and initialled by the supervisor.

Analytical test report

17.3 The analytical test report (see Appendix 1) is a compilation of the results and states the conclusions of the examination of a sample. It must be:

(a) issued by the laboratory;

(b) based on the analytical worksheet (see Part Three, section 15).

Content of the analytical test report

17.4 The analytical test report must provide the following information (see Appendix 1):

(a) the registration number of the sample;

(b) the name and address of the laboratory testing the sample;

(c) the name and address of the originator of the request for analysis;

(d) the name and description and batch number of the sample, where appropriate;

(e) a reference to the specifications used for testing the sample, including the limits;

(f) the results of all the tests performed, or the numerical results of all the tests performed (if applicable);

(g) a conclusion whether or not the sample was found to be within the limits of the specifications used;

(h) the date on which the test was performed;

(i) the signature of the head of the laboratory or authorized person;

(j) the name and address of the repacker and/or trader, if applicable;

(k) the name and address of the original manufacturer;

(l) whether or not the sample complies with the requirements;

(m) the date on which the sample was received;

(n) the expiry date.

18. Retained samples

18.1 Samples are retained for at least 6 months if they are found to comply with the requirements and for at least 12 months or until their expiry date (whichever is longer) in the case of non-compliance (for storage, see Part Three, section 14.11).

Part Four. Safety

19. General rules

19.1 General and specific safety instructions must be made available to each staff member and supplemented regularly as appropriate (e.g. with written material, poster displays, audiovisual material and occasional seminars).

19.2 General rules for safe working in accordance with national regulations and SOPs normally include the following requirements:

(a) safety data sheets must be available to staff before testing is carried out;

(b) smoking, eating and drinking in the laboratory must be prohibited;

(c) staff must be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;

(d) staff must wear laboratory coats or other protective clothing, including eye protection;

(e) special care must be taken, as appropriate, in handling, for example, highly potent, infectious or volatile substances;

(f) all containers of chemicals must be fully labelled and include prominent warnings (e.g. “Poison”, “Flammable”, “Radiation”, etc.) whenever appropriate;

(g) adequate insulation and spark-proofing must be provided for electrical wiring and equipment, including refrigerators;

(h) safety rules in handling cylinders of compressed gases must be observed, and staff must be familiar with the relevant colour identification codes;

(i) staff must be aware of the need to avoid working alone in the laboratory;

(j) first-aid materials must be provided, and staff instructed in first-aid techniques, emergency care and the use of antidotes.

19.3 Protective clothing must be available, including eye protection, masks and gloves. Water showers should be installed. Rubber suction bulbs must be used on manual pipettes and siphons. Staff must be instructed in the safe handling of glassware, corrosive reagents and solvents, and particularly in the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions must be given for work with violent, uncontrollable or

dangerous reactions when handling specific reagents (e.g. mixing water and acids, or acetone–chloroform and ammonia), flammable products, oxidizing or radioactive agents, and especially biologicals such as infectious agents. Peroxide-free solvents should be used. Staff must be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts (see also Part One, section 7.14).

19.4 Poisonous or hazardous products must be singled out and labelled appropriately, but it must not be taken for granted that all other chemicals and biologicals are safe. Unnecessary contact with reagents, especially solvents and their vapours, must be avoided. The use of known carcinogens and mutagens must be limited or totally excluded if required by local regulations. Replacement of toxic solvents and reagents by less toxic materials or reduction of their use must always be the aim, particularly when new techniques are developed.

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Appendix 1

Model analytical test report for active pharmaceutical ingredients, excipients and pharmaceutical products

Registration no.:[1] _____

Name and address of laboratory testing the sample:

_____

_____

_____

Name and address of originator requesting analysis (if applicable):

_____

_____

_____

Sample information

Name of product (INN,[2] brand name(s), etc.):

_____

Dosage form (if applicable): _____

Concentration or strength (if applicable): _____

Marketing authorization number (if applicable): _____

Description (appearance of container and contents):

_____

_____

_____

Batch number(s): _____

Required storage conditions (if applicable): _____

Date received: _____

Date of manufacture (if known): _____

Expiry date (for pharmaceutical products) or retest date (for starting materials or pharmaceutical excipients): _____

Name and address of original manufacturer:

Telephone: _____ Fax: _____

Name and address of repacker/trader (if applicable):

Telephone: _____ Fax: _____

Test procedure (reference) (if applicable)	Result (numerical) (if applicable)	Acceptance criteria (limits)

Conclusions

Compliance with acceptance criteria: yes ☐ no ☐

Date test performed/finalized: _____

Name and address of head of laboratory/authorized person:

Telephone: _____ Fax: _____

Signature: _____

Explanatory notes

[1] Of sample or analytical test report.
[2] The International Nonproprietary Name should be used whenever possible.

Appendix 2

Equipment for a first-stage and medium-size pharmaceutical control laboratory

A list of equipment considered by the Committee to be adequate either for a first-stage or medium-size pharmaceutical control laboratory is given below.

National drug regulatory authorities or laboratories wishing to perform pharmaceutical analyses should consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons, it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel charges. Experience has shown that for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Guidance and information on the cost of equipment can be obtained from the Secretariat.

First-stage laboratory

Equipment and major instruments	*Quantity*
Top-loading balance	1
Analytical balance, semi-micro (4 digits)	1
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope (binocular)	1
Polarimeter (manual)	1
High-performance liquid chromatograph with ultraviolet detector	1
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Equipment for thin-layer chromatography (TLC), including spreader	1
TLC spotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1

Disintegration test equipment (1 basket for 6 tablets)	1
Soxhlet extraction apparatus (60 ml)	1
Micrometer callipers	1
Pycnometers	2
Burettes	5
Desiccator	1
Centrifuge (table-top model, 4-place swing rotor)	1
Water-bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1

Optional items

Analytical balance, micro (5 digits)	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water-bath	1
Ultrasonic cleaner (5 litres)	1

Medium-size laboratory

General laboratory equipment	***Quantity***
Top-loading balance	1 or 2
Analytical balance, semi-micro (4 digits)	2
Analytical balance, micro (5 digits)	1

Microscope (binocular)	1 or 2
Equipment for TLC, including spreader	1
TLC multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Potentiometric titrimeter	1
Micro-Kjeldahl equipment (including fume flasks)	1
Burettes	6
Micrometer callipers	1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 ml)	6
Sieves (assorted sizes)	2 sets
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water-bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1 or 2
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	1
Freezer	1
Ultrasonic cleaners (5 litres)	2
Ultrasonic pipette cleaner	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Major instruments	
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength ultraviolet/visible detector	1

Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct head space)	1
Refractometer	1
Karl Fischer titrator	1
Potentiograph	1
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1

Optional items

Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph:	1
— with fluorescence detector	1
— with diode-array detector	1
— with refractive index detector	1
— with conductivity detector	1
TLC scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1

Equipment for microbiology unit

pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2
Membrane filter assembly for sterility tests	1
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	2 or 3
Anaerobic jar	1
Zone reader	1
Centrifuge	1

Water-bath (thermostatically controlled)	2
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freezer	1
Cleaning device for glassware, including pipettes	2

WHO Technical Report Series, No. 902, 2002

Annex 4
Considerations for requesting analysis of drug samples[1]

Many WHO Member States do not have adequate drug quality control facilities of their own. For drugs imported into such countries, manufacturers' batch certificates issued in accordance with the WHO Certification Scheme (*1*) will normally provide sufficient information on the quality and origin of a product. This assumes that an official inspection of the manufacturing site has been performed and that the manufacturer complies with good manufacturing practices (*2*). For domestically manufactured pharmaceuticals, manufacturers' batch certificates may be relied upon to indicate the quality of a product. This implies that the results of an inspection by the competent national authority have shown that the manufacturer is capable of reliably producing a product of the required quality.

However, in certain situations a need may arise for national authorities to test drug samples when testing facilities are not available. For this purpose, laboratories in other countries or contract laboratories in the same or in another country may be contacted (for a model certificate of analysis, see Annex 10). General considerations before approaching them are set out below.

Important note: **Any laboratory contacted has the right to decline a request for analysis without furnishing any explanation or remark.**

Reason for analysis

Full-scale pharmacopoeial testing is expensive. The national authority may prefer to limit analysis to those products which:

— show physical signs of instability or deterioration (*3*);
— are of unidentifiable origin;
— emanate from a supplier suspected of dealing in substandard products;
— have given rise to disputed analytical results;
— are suspected of causing adverse reactions;

[1] These considerations are applicable to national drug regulatory authorities, but may also apply to the independent analysis of pharmaceuticals in trade.

— will be used as evidence in litigation;
— are provided through drug donations.

Where the information on the quality of a product is important and needs to be communicated rapidly (such as the presence of products of deterioration or a new impurity profile), selected purity tests may be performed instead of full-scale pharmacopoeial testing. These tests should include a potency test, and any tests additional to those in the pharmacopoeial monograph that might be required. Since the selected tests may not always be capable of detecting all the impurities of unknown source, a combination of analytical methods, such as several different chromatographic methods or differential scanning calorimetry together with gas or liquid chromatography, could be used. The suitability of the pharmacopoeial monograph from the point of view of the detection of impurities should be evaluated, especially if the drug is from a new source, which may cause it to have a different impurity profile. If necessary, the advice of an experienced laboratory should be sought.

Communication before samples are submitted

Before a sample of a product is sent to a laboratory in another country or a contract laboratory and its analysis is requested, the laboratory concerned must be asked whether it is willing to carry out the analysis. The request should be accompanied, as a minimum, by the following information, which should be given in writing:

— the reason(s) for the request;
— the name and address of the manufacturer and/or distributor;
— the marketing authorization and its number or reference;
— the pharmaceutical dosage form;
— the composition of the product (using International Nonproprietary Names (INNs), where possible);
— the concentration or strength;
— the date of manufacture;
— details of the storage conditions and the expiry date;
— any background information about the route of synthesis of the ingredients, if available;
— a reference to pharmacopoeial or other specifications, including details of the analytical methods that should be used;
— the purpose of the analyses;
— the number of separate samples to be analysed and their batch (lot) number(s);
— the proposed mode of payment for the analysis;
— the preferred language and format of the report containing the results (see below).

It is recommended that a contract between the requesting party and the laboratory that will perform the tests should be drawn up to settle issues such as liability, and the mode of payment for the expenses involved. The responsibilities of the two parties should be defined. The laboratory that has been contacted should indicate, at the earliest possible opportunity, its decision whether or not to undertake the analyses.

If the laboratory agrees to undertake the analysis, the following should be communicated to the requesting party:

— the nature and size of the sample required;
— any additional non-pharmacopoeial tests which may be required;
— the cost and the mode of payment;
— a tentative estimate of the time that the analysis will take;
— the method to be used to transmit the results.

Submission of samples

Upon agreement with a laboratory, the sample should be dispatched by the national drug regulatory authority or the requesting party. The sample must be suitably packaged and labelled (*4*). It should be divided into two portions, each of which must be properly packed and sealed. The laboratory should analyse one sealed portion only, and retain the other for presenting during litigation or investigation. In the case of products that are subject to legal controls on exportation, appropriate arrangements must be made by the national drug regulatory authority to ensure due compliance with customs requirements.

Analytical results

All analyses undertaken by a laboratory should be in accordance with the specified pharmacopoeial or other specifications mentioned in the request for analysis, or as subsequently agreed (see Annex 3). If requested, results of the analyses can be transmitted by facsimile or other means (e.g. electronic mail), and confirmed with a detailed signed report. The report should be in the working language of the laboratory, or as agreed between the parties (see Annex 3).

References

1. Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 10 (WHO Technical Report Series, No. 863).

2. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second*

report. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).

3. *The international pharmacopoeia*, 3rd ed. *Vol. 4. Tests, methods, and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms*. Geneva, World Health Organization, 1994.
4. Sampling procedure for industrially manufactured pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990, Annex 2 (WHO Technical Report Series, No. 790).

WHO Technical Report Series, No. 902, 2002

Annex 5
Basic elements of good manufacturing practices in pharmaceutical production

Poor-quality medicines are not only a health hazard, but a waste of money for both governments and individual consumers, since they may contain toxic substances that have been unintentionally added. For example, in Haiti in 1996, more than 80 children died after receiving a syrup for cough and colds containing glycerol contaminated with diethylene glycol (*1*). If the manufacturer had followed good manufacturing practices (GMP), these deaths could have been prevented.

In addition, a medicine that contains little or none of the claimed active ingredient will not have the intended therapeutic effect. An antibiotic with some — but not enough — of the active ingredient will not cure infections. Even worse, bacteria exposed to low levels of the antibiotic may not be killed and may become resistant to the drug, even at the correct dosage, putting more lives at risk.

Good manufacturing practices help boost pharmaceutical export opportunities

Most countries will accept the import and sale of medicines only if they have been manufactured according to internationally recognized GMP. For this reason, governments seeking to promote their country's export of pharmaceuticals can do so by making GMP mandatory for all pharmaceutical production and by training their inspectors in GMP requirements.

What are good manufacturing practices?

GMP are that part of quality assurance which ensures that products are consistently produced and controlled according to quality standards. They are designed to minimize the main risks involved in pharmaceutical production that cannot be eliminated through testing of the final product. These risks are:

— the unexpected contamination of products, causing damage to health or even death;
— incorrect labels on containers, which could mean that patients receive the wrong medicine;
— insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects.

GMP cover all aspects of production, from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. Systems must be established to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process — every time a product is made.

WHO has established detailed guidelines for GMP (*2*), and many countries have formulated their own GMP requirements based on those of WHO. Others have harmonized their requirements, e.g. in the Association of South-East Asian Nations (ASEAN), in the European Union and through the Pharmaceutical Inspection Convention.

Are good manufacturing practices necessary if there is a quality control laboratory?

Good quality must be built in during the manufacturing process; testing products after they have been manufactured is not enough. GMP prevent errors that cannot be eliminated through quality control of the finished product. Without GMP it is impossible to be sure that every unit of medicine is of the same quality as those tested in the laboratory.

> In the early 1970s, a manufacturer in the United Kingdom produced an infusion fluid which caused the death of five patients because it was heavily contaminated with bacteria (*3*). Before distributing the fluid, the manufacturer had tested several bottles and found them to be sterile. Eventually a technical fault was found in the sterilizer: the bottles at the bottom had not been properly sterilized. The bottles that the manufacturer had tested were from the upper part, giving the false impression that all the bottles were sterile.

Can manufacturers afford to implement good manufacturing practices?

Making poor-quality products does not save money. In the long run, it is more expensive finding mistakes after they have been made than preventing them in the first place. GMP are designed to ensure that mistakes do not occur.

Implementation of GMP is an investment in good-quality medicines, and will improve the health of both the individual patient and the community, as well as benefiting the pharmaceutical industry and health professionals.

Making and distributing poor-quality medicines leads to loss of credibility for everyone, including public and private health care services and pharmaceutical manufacturers.

References

1. Fatalities associated with ingestion of diethylene glycol — contaminated glycerol used to manufacture acetaminophen syrup — Haiti, November 1995–June 1996. *Morbidity and Mortality Weekly Report*, 1996, **45**(30):649–650.
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
3. Meers PD et al. Intravenous infusion of contaminated dextrose solution: the Devonport incident. *Lancet*, 1973, **ii**(7839):1189–1192.

WHO Technical Report Series, No. 902, 2002

Annex 6
Good manufacturing practices for sterile pharmaceutical products

Introductory note

This document is a revision of section 17 of Part Three of "Good manufacturing practices [GMP] for pharmaceutical products" (*1*), which emphasizes specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate and pyrogen contamination. It is not exhaustive in character, and some technical requirements may change in line with developments in the field of GMP or advances in engineering design.

1. General considerations

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and

sterilization should be carried out in separate areas within a clean area. These areas are classified into four grades (see section 4.1).

1.3 Manufacturing operations are divided here into two categories: first, those where the product is terminally sterilized, and second, those which are conducted aseptically at some or all stages.

2. Quality control

2.1 Samples taken for sterility testing should be representative of the whole of the batch, but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

(a) for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;

(b) for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

2.2 The sterility of the finished product is ensured by validation of the sterilization cycle in the case of terminally sterilized products, and by "media-fills" runs for aseptically processed products. Batch processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods must be used for the validation and performance of the sterility test.

2.3 For injectable products, the water for injection and the intermediate and finished products should be monitored for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of such failure should be investigated and remedial action taken where necessary.

3. Sanitation

3.1 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written programme. Monitoring should be regularly undertaken in order to detect the emergence of resistant strains of microorganisms. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection.

Table 1
Limits for microbiological contamination[a]

Grade[b]	Air sample (CFU/m^3)	Settle plates (diameter 90 mm) (CFU/4 hours)[c]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	<3	<3	<3	<3
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

[a] These are average values. The grades are defined in section 4.1.
[b] The airborne particulate classification for the four grades is given in Table 2.
[c] Individual settle plates may be exposed for less than 4 hours.

3.2 Disinfectants and detergents should be monitored for microbiological contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in grade A and B areas (see section 4.1) should be sterilized before use.

3.3 In order to control the microbiological cleanliness of the various grades in operation, the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent and methods such as settle plates, and volumetric air and surface sampling (e.g. swabs and contact plates) should be used. The zones should not be contaminated through the sampling methods used in the operations. The results of monitoring should be considered when batch documentation for release of the finished product is reviewed. Both surfaces and personnel should be monitored after critical operations.

3.4 Levels (limits) of detection of microbiological contamination should be established for alert and action purposes, and for monitoring the trends in air quality in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 1. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

4. Manufacture of sterile preparations

4.1 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbiological contamination of the product or materials being handled.

Table 2
Airborne particulate classification for manufacture of sterile pharmaceutical preparations

Grade	At rest		In operation	
	Maximum number of particles permitted/m^3		Maximum number of particles permitted/m^3	
	0.5–5.0 μm	>5.0 μm	0.5–5.0 μm	>5.0 μm
A	3500	0	3500	0
B	3500	0	350000	2000
C	350000	2000	3500000	20000
D	3500000	20000	Not defined	Not defined

In order to meet "in operation" conditions, these areas should be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state. This latter state is the condition where the installation is complete, and production equipment has been installed and is operating, but no operating personnel are present. The "in operation" state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel are present.

For the manufacture of sterile pharmaceutical preparations, four grades are distinguished here, as follows:

- *Grade A*: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are provided by a laminar-airflow workstation. Laminar-airflow systems should provide a homogeneous air speed of approximately 0.45 m/s ± 20% (guidance value) at the working position.
- *Grade B*: In aseptic preparation and filling, the background environment for the grade A zone.
- *Grades C and D*: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for the four grades is given in Table 2.

To obtain air of the required characteristics, methods specified by national authorities should be used. It should be noted that:

- In order to reach the B, C and D air grades, the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it. At least 20 air changes per hour are usually required for a room with a good airflow pattern and appropriate high-efficiency particulate air (HEPA) filters.

Table 3
Comparison of different airborne particulate classification systems for clean areas[a]

WHO (GMP)	United States (209E)	United States (customary)	ISO/TC (209)	EEC (GMP)
Grade A	M 3.5	Class 100	ISO 5	Grade A
Grade B	M 3.5	Class 100	ISO 5	Grade B
Grade C	M 5.5	Class 10 000	ISO 7	Grade C
Grade D	M 6.5	Class 100 000	ISO 8	Grade D

EEC: European Commission; ISO/TC: International Organization for Standardization Technical Committee.
[a] Source: references 1–4.

- Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. is not given here. Reference should be made to other guidelines published in compendia such as the European, Japanese or United States pharmacopoeias, or in documents issued by the European Committee for Standardization and the International Organization for Standardization (ISO).

The different airborne particulate classification systems for clean areas are shown in Table 3.

4.2 The particulate conditions given in Table 2 for the "at rest" state should be achieved in the absence of the operating personnel after a short "clean-up" period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 2 for grade A "in operation" should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

4.3 In order to control the particulate cleanliness of the various clean areas during operation, they should be monitored.

4.4 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, the appropriate corrective actions should be taken, as prescribed in the operating procedures.

4.5 The area grades as specified in sections 4.6–4.14 must be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. sterile media fills). The determination of an appropriate process area environment and

a time limit should be based on the microbiological contamination (bioburden) found.

Terminally sterilized products

4.6 Components and most products should be prepared in at least a grade D environment in order to give low microbial and particulate counts, suitable for filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily not processed mainly in closed vessels), the preparation should generally be done in a grade C environment.

4.7 The filling of products for terminal sterilization should generally be done in at least a grade C environment.

4.8 Where the product is at unusual risk of contamination from the environment (e.g. because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling should be done in a grade A zone with at least a grade C background.

4.9 The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

Aseptic preparation

4.10 Components after washing should be handled in at least a grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be done in a grade A environment with a grade B background.

4.11 The preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not sterile filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.

4.12 The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be done in a grade A environment with a grade B background.

4.13 The transfer of partially closed containers, as used in freeze–drying, should, before stoppering is completed, be done either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.

4.14 The preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment with a

grade B background when the product is exposed and is subsequently filtered.

Processing

4.15 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

4.16 Preparations containing live microorganisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines consisting of dead organisms or of bacterial extracts may be dispensed into containers, after validated inactivation and validated cleaning procedures, in the same premises as other sterile pharmaceutical products.

4.17 The validation of aseptic processing should include simulating the process using a nutrient medium. The form of the nutrient medium used should generally be equivalent to the dosage form of the product. The process-simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. Consideration should be given to simulation of the worst expected condition. The process-simulation test should be repeated at defined intervals and after any significant modification to the equipment and process. The number of containers used for a medium fill should be sufficient to ensure a valid evaluation. For small batches, the number of containers for the medium fill should be at least equal to the size of the product batch.

4.18 Care should be taken to ensure that any validation does not compromise the processes.

4.19 Water sources, water-treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken.

4.20 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum, and the movement of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

4.21 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.

4.22 Components, bulk-product containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated. The stage of processing of components, bulk-product containers and equipment should be properly identified.

4.23 The interval between the washing and drying and the sterilization of components, bulk-product containers and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

4.24 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.

4.25 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.

4.26 The bioburden of products should be monitored before sterilization. There should be a working limit on the contamination of products immediately before sterilization that is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large-volume parenterals, should be passed through a microorganism-retaining filter, if possible immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets should be protected, e.g. by hydrophobic microbiological air filters.

4.27 Components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress should be sterilized and, wherever possible, passed into the area through double-ended sterilizers sealed into the wall. Other procedures that prevent the introduction of contamination (e.g. triple wrapping) may be acceptable in some circumstances.

4.28 The efficacy of any new processing procedure should be validated, and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

5. Sterilization

5.1 Whenever possible, products intended to be sterile should preferably be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal sterilization by heating due to the instability of a formulation, a decision should be taken to use an

alternative method of terminal sterilization following filtration and/or aseptic processing.

5.2 Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (but not with ultraviolet radiation unless the process is thoroughly validated), by ethylene oxide (or other suitable gaseous sterilizing agents) or by filtration with subsequent aseptic filling of sterile final containers. Each method has its particular advantages and disadvantages. Where possible and practicable, heat sterilization is the method of choice.

5.3 The microbiological contamination of starting materials should be minimal, and their bioburden should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

5.4 All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeial or other national standards or when it is used for a preparation that is not a simple aqueous or oily solution.

5.5 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators, where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

5.6 For effective sterilization, the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved.

5.7 Biological indicators should be considered only as an additional method of monitoring the sterilization process. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid any transfer of microbiological contamination from them.

5.8 There should be a clear means of differentiating products that have not been sterilized from those that have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number, and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch

(or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the batch is, in fact, sterile.

5.9 Sterilization records should be available for each sterilization run. They should be approved as part of the batch-release procedure.

6. Terminal sterilization

Sterilization by heat

6.1 Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/temperature chart with a suitably large scale. The temperature should be recorded by a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. The chart, or a photocopy of it, should form part of the batch record. Chemical or biological indicators may also be used but should not take the place of physical controls.

6.2 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time must be determined for each type of load to be processed.

6.3 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized.

Sterilization by moist heat

6.4 Sterilization by moist heat (heating in an autoclave) is suitable only for water-wettable materials and aqueous formulations. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which should be routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

6.5 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after

sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

6.6 Care should be taken to ensure that the steam used for sterilization is of suitable quality and does not contain additives at a level that could cause contamination of the product or equipment.

Sterilization by dry heat

6.7 Sterilization by dry heat may be suitable for non-aqueous liquids or dry powder products. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied, it should be passed through a microorganism-retaining filter (e.g. an HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins will be required as part of the validation.

Sterilization by radiation

6.8 Sterilization by radiation is used mainly for the sterilization of heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

6.9 If sterilization by radiation is carried out by an outside contractor, the manufacturer is responsible for ensuring that the requirements of section 6.8 are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g. for using the correct dose) should also be specified.

6.10 During the sterilization procedure, the radiation dose should be measured. For this purpose, the dosimeters used must be independent of the dose rate and must provide a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are employed, they should be used within the time-limit of their calibration. Dosimeter absorbances should be read shortly after exposure to radiation. Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

6.11 Validation procedures should ensure that consideration is given to the effects of variations in the density of the packages.

6.12 Handling procedures should prevent any misidentification of irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

6.13 The total radiation dose should be administered within a predetermined period of time.

Sterilization by gases and fumigants

6.14 This method of sterilization should only be used for products where there is no suitable alternative.

6.15 Various gases and fumigants may be used for sterilization (e.g. ethylene oxide, hydrogen peroxide vapour). Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. These limits should be incorporated in the specifications.

6.16 Direct contact between gas and microorganisms is essential; precautions should therefore be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

6.17 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. This requirement should be balanced against the need to minimize the waiting time before sterilization.

6.18 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

6.19 Biological indicators should be stored and used according to the manufacturer's instructions, and their performance checked by positive controls.

6.20 For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process, and of the gas concentration. The pressure and temperature should be recorded on a chart throughout the cycle. The records should form part of the batch record.

6.21 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow concentrations of residual gas and reaction products to fall to their prescribed levels. This process should be validated.

7. Aseptic processing and sterilization by filtration

7.1 The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods (see sections 5 and 6).

7.2 The operating conditions should be such as to prevent microbial contamination.

7.3 In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to: (a) the environment; (b) the personnel; (c) the critical surfaces; (d) the container/closure sterilization and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilizing filter.

7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 µm (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

7.5 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

7.6 The fibre-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters must not be used under any circumstances.

7.7 The integrity of the filter should be checked by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test, immediately after use (it may also be useful to test the filter in this way before use). The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation, and any significant differences from these values should be noted and investigated. The results of these checks should be recorded in the batch record. The integrity of critical

gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. Consideration should be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high-temperature air.

7.8 The same filter should not be used for more than 1 working day unless such use has been validated.

7.9 The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

8. Personnel

8.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside such areas as far as possible.

8.2 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

8.3 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

8.4 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbiological hazards should be decided by a designated competent person.

8.5 Outdoor clothing should not be brought into clean areas, and personnel entering changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure designed to minimize the contamination of clean area clothing or the carry-through of contaminants to clean areas.

8.6 Wrist-watches and jewellery should not be worn in clean areas, and cosmetics that can shed particles should not be used.

8.7 The clothing worn and its quality should be appropriate for the process and the grade of the working area (workplace). It should be worn in such a way as to protect the product from contamination. The clothing required for each grade is as follows:

- *Grade D*. The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.
- *Grade C*. The hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.
- *Grades A/B*. Headgear should totally enclose the hair and, where relevant, beard and moustache. A single or two-piece trouser suit, gathered at the wrists and with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A face mask should be worn to prevent the shedding of droplets. Appropriate, sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

8.8 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B room, clean sterilized or adequately sanitized protective garments should be provided at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary.

8.9 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

9. Premises

9.1 All premises should, as far as possible, be designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas

should be designed so that all operations can be observed from outside.

9.2 In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

9.3 To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.

9.4 False ceilings should be sealed to prevent contamination from the space above them.

9.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.

9.6 Sinks and drains should be avoided wherever possible and should be excluded from grade A/B areas where aseptic operations are carried out. Where installed, they should be designed, located and maintained so as to minimize the risks of microbiological contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent back-flow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbiological contaminants.

9.7 Changing rooms should be designed as airlocks and used to separate the different stages of changing, thus minimizing particulate and microbiological contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes necessary. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.

9.8 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system can be installed to prevent the opening of more than one door at a time.

9.9 A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 pascals (guidance value). Particular attention should be paid to the protection of the zone of greatest risk,

i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

9.10 It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk.

9.11 A warning system should be included to indicate failure in the air supply. An indicator of pressure difference should be fitted between areas where this difference is important, and the pressure difference should be regularly recorded.

9.12 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. grade A filling zones, by means of a physical barrier.

10. Equipment

10.1 A conveyor belt should not pass through a partition between a grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel).

10.2 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

10.3 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be resterilized after complete reassembly, wherever possible.

10.4 When equipment maintenance is carried out within a clean area, clean instruments and tools should be used, and the area should be cleaned and disinfected again, where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

10.5 All equipment, including sterilizers, air-filtration systems, and water-treatment systems, including stills, should be subject to planned

maintenance, validation and monitoring; its approved use following maintenance work should be documented.

10.6 Water-treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Consideration should be given to including a testing programme in the maintenance of a water system. Water for injection should be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70 °C or not more than 4 °C.

11. Finishing of sterile products

11.1 Containers should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.

11.2 Containers sealed under vacuum should be sampled and the samples tested, after an appropriate predetermined period, to ensure that the vacuum has been maintained.

11.3 Filled containers of parenteral products should be inspected individually. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. The results should be recorded.

References

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WHO Technical Report Series, No. 902, 2002

Annex 7
Guidelines on pre-approval inspections

1. General

The advice provided here extends that given in the "Provisional guidelines on the inspection of pharmaceutical manufacturers" (*1*). The objectives of an inspection, as given in the introduction to the guidelines, are:

— to control and enforce compliance with general good manufacturing practices (GMP) (*2*); and
— to authorize the manufacture of specific pharmaceutical products, normally in response to a licensing application.

These guidelines are applicable mainly to inspections of the first type, whether performed as a condition for the issue of a manufacturing licence/authorization, or on a periodic, routine basis. They are essentially concerned with inspections of manufacturing and quality-control facilities conducted before a marketing authorization (product licence or registration) for a pharmaceutical product is granted.

2. Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

application
A marketing authorization for a new drug application.

manufacturer
A company that carries out at least one step of manufacture (*2*).

manufacture
All operations concerned with the purchase of materials and products, production (including packaging), quality control, release, storage, the distribution of pharmaceutical products, and the related controls (*2*).

method validation/verification
Method validation is conducted where non-compendial analytical methods are included in the application to confirm that the applicants' proposed analytical methods are suitable for regulatory purposes. A side-by-side comparison with a compendial method, if available, should be included. Method verification is conducted where the methods are compendial, to confirm whether the product as compounded can be analysed satisfactorily by the official method.

pre-approval batches
Pilot or laboratory-scale batches, upon which the application is based, e.g. batches used for pivotal clinical trials and/or those used for bioavailability, bioequivalence and stability studies, and scale-up batches.

3. Objectives

Before any application is approved, it is necessary to determine whether all establishments participating in the manufacture of the finished dosage form are in compliance with GMP and the application commitments. Pre-approval inspections have the following specific objectives:

- Evaluation of the establishment's compliance with GMP requirements, particularly regarding proper environment, quality management, personnel, facilities and equipment.
- Evaluation of the procedures and controls implemented in the manufacture of the product (pre-approval batches), to determine whether they are in conformity with the application commitments.
- Audit of the completeness and accuracy of the manufacturing and testing information submitted with the application, and of the conformity of pre-approval batches with planned commercial batches (process validation protocol).
- The collection of samples for the validation or verification of the analytical methods included in the application.

4. Priorities

Pre-approval inspections are considered to be an important part of the application review and approval process. However, since this represents a considerable workload, inspections are not normally carried out routinely, but rather only in specific cases where non-compliance is possible. Thus inspections may be required for:

— new chemical entities;
— drugs of narrow therapeutic range, and drugs for serious conditions requiring an assured therapeutic response;
— products previously associated with serious adverse effects, complaints, recalls, etc.;
— products that are difficult to manufacture or test, or that are of doubtful stability (and therefore associated with the risk of defects);
— new applicants or manufacturers; and
— applications from manufacturers who have previously failed to comply with GMP or official quality specifications.

For other applications, the drug regulatory authority will rely on the results of recent inspections of the applicant's or manufacturer's facilities for the production of dosage forms similar to that of the proposed product.

5. Preparation for the inspection

An inspection team should, where possible, include analysts and other specialists, e.g. in pharmaceutical technology, or if available, persons with expertise in these fields, when needed. Team members may be assigned to inspect new operations or manufacturing sites associated with product failures. When possible, the analyst involved in the laboratory evaluation of the product under review should participate in the inspection. Pre-approval inspection is often carried out by a single inspector.

It is necessary to verify that the applicant holds an appropriate manufacturing authorization and that manufacturing is carried out in conformity with that authorization (licence).

An essential step in the review of applications is determining whether the commitments made by the manufacturer are reflected in actual practice. A review of the application information is also important in preparing for inspections of firms or processes with which the inspector is unfamiliar. The drug regulatory authority should provide inspectors with relevant information on the application. (Some countries request an additional copy of this information from applicants which is forwarded to the inspection team.) The information

provided should include a copy of the manufacturing and controls section of the application, together with information relating to pre-approval batches.

Reasonable efforts should be made to conduct pre-approval inspections at the earliest possible opportunity, since unnecessary delays will prevent the timely review of applications. However, in some facilities the development or the manufacturing processes may not have been completed. In addition, changes may have occurred in the status of the application, e.g. major deficiencies in the application or the closure of an ancillary facility may affect the need for an inspection. In any case, the timing of the inspection should be coordinated between the inspectorate and the applicant.

For the inspection of major new facilities involving many applications, special coordination efforts are often beneficial.

When desirable, pre-approval inspections should be coordinated with the laboratory scheduled for method validation so as to enable it to participate in the inspection and in the collection of samples.

6. Carrying out the inspection

Emphasis should be placed on the evaluation of the manufacturing process, including data verification and the assessment of compliance with GMP. The production and control procedures described in the application must be compared with those used for the manufacture of pre-approval batches. If warranted by records of past label mix-ups, packaging and labelling control procedures should be evaluated. A programme of ongoing stability testing needs to be addressed.

The inspection team will determine whether the application provides the scientific data justifying full-scale production procedures and controls. The validation of pertinent manufacturing procedures, including equipment qualification, will also be evaluated.[1] However, inspectors should not recommend withholding approval of applications based on a lack of complete full-scale, multiple-batch validation of sterile and non-sterile processes, unless the data submitted in the application are found to be of questionable validity or completeness. It should be understood that full-scale validation may be completed after approval of the application, but before shipment of the first commercial batches. Nevertheless, certain data must be included in the application to demonstrate that the sterilization or aseptic fill process has been qualified. The inspection team is expected to audit the data to determine their authenticity, accuracy and completeness.

[1] For details of recommended validation programmes, see reference *3*.

Investigational products are often produced in facilities other than those used for full-scale production (*4*). These facilities and the associated manufacturing and control procedures are not routinely inspected unless validation of the transfer of the methods from the "investigational" facilities to the full-scale facilities is lacking or questionable. The facilities may be periodically inspected when this is required by national legislation/regulation.

All suppliers and manufacturers of starting materials used in the formulation of pre-approval batches should be identified. The physical characteristics and specifications of the drug substance should be reviewed. This is particularly important for solid oral dosage forms where the physical characteristics of the drug substance often affect uniformity, dissolution and absorption of the dose.

When a pharmaceutical manufacturer replaces the supplier or manufacturer of the drug substance used for the manufacture of the pre-approval batches by another supplier or manufacturer, the application should include data demonstrating that the dosage forms formulated with the drug substance from the two different sources are equivalent in terms of conformity with established specifications, including those given in the application. Specifications should also cover the physical characteristics of the drug substances.

The addition of any new drug substance and/or dosage form to a production environment must be carefully evaluated in terms of its impact on other products already under production. Any changes that may be necessary in the building and facility must be assessed for their effect on overall compliance with GMP requirements. For example, a new toxic, potent or highly sensitizing product may require additional measures against cross-contamination, and facilities already operating at full capacity may not have adequate space for additional products. The evaluation should also include an assessment of whether any change in the manufacturing authorization is necessary.

Laboratory equipment and procedures must be qualified and validated. Every pre-approval inspection should include an evaluation of laboratory controls and procedures, and a review of some of the raw data used to generate results. The authenticity and accuracy of the data used in the development of a test method should be reviewed.

The inspection team should pay special attention to any newly established facilities, newly installed equipment and/or new raw material suppliers. If unapproved facilities are in use, this should be reported immediately. Inspections of these facilities are not normally required.

7. Sample collection and testing

The pre-approval inspection may include the collection of samples for validation of the analytical methods. Normally the sample size should be sufficient for three full analyses. Unless otherwise indicated by the laboratory, samples of the following sizes may be taken, depending on the dosage form of the product:

— tablets and capsules: 300 units of production;
— injections (single component): 100 units of production;
— injections (combination): 100 units of production plus 10 samples of each component;
— oral powders for reconstitution: 10 units of production;
— oral liquids: 1 litre.

It is important to collect, with the samples, the relevant manufacturer's analytical documentation, namely a copy of the analytical methods used by the inspected laboratory and the report of the analyses performed by the applicant on the batch sampled. A method validation report may be of some use in better understanding and reproducing the analytical methods. Problems encountered in the performance of the analyses may be resolved by an exchange of information between the applicant and the government laboratory.

Samples are tested in accordance with methods described in the application. If there are problems with the methods that require additional information from the applicant, the laboratory director must review the situation and decide whether the applicant should be contacted. The written request should be included in the documentation submitted to the review analyst.

Each method validation/verification report should contain the following:

- The identification of the test samples received, a description of the product tested, and confirmation of conformity with the product described in the application.
- The original analytical worksheets with calculations, the results of all tests performed, comments by the analyst(s), associated spectra, chromatograms, etc., and a comparison of the results obtained with the applicant's data and with the applicable specifications.
- An evaluation of each test performed by the applicant and the laboratory.
- A recommendation as to whether the methods are acceptable, acceptable only after specified changes have been made, or unacceptable.

If samples have not been collected in the course of a pre-approval inspection, the results of the analytical examination of the samples

submitted by the applicant may nevertheless be used as supporting information.

The reserve samples, associated documentation and copies of laboratory reports should be stored in an orderly and retrievable way for a time period specified by national regulations. It is usually recommended that all material should be kept for a minimum of 3 years or for 1 year after the expiry date of the finished product.

8. Follow-up regulatory/administrative decisions

The inspectorate (inspection group of the drug regulatory authority) should recommend withholding approval when significant deviations from GMP requirements and other application commitments have occurred having an adverse effect on the product covered by the application. Examples of significant problems are:

- Misrepresentation of data or conditions relating to pre-approval batches.
- Pre-approval batches not manufactured in accordance with GMP.
- Inconsistencies and/or discrepancies raising significant questions concerning the validity of the records.

If applications are refused because of significant non-compliance with GMP, action must be taken to ensure that the necessary corrective measures are taken.

The drug regulatory authority is expected to advise the applicant that the inspectorate has recommended withholding approval of the application and give the reasons for this recommendation.

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WHO Technical Report Series, No. 902, 2002

Annex 8
Quality systems requirements for national good manufacturing practice inspectorates

Background

Following the provisional guidelines on the inspection of pharmaceutical manufacturers (*1*), the WHO Expert Committee on Specifications for Pharmaceutical Preparations acknowledged that additional guidelines concerning national inspectorates would be of value in strengthening the implementation of good manufacturing practices (GMP) (*2*) and enhancing mutual recognition among inspectorates.

A trend has recently become apparent in WHO Member States for non-commercial institutions, such as certification bodies, testing

laboratories, etc., to introduce quality systems principles in their internal operations. The same principles are also being applied by governmental pharmaceutical inspectorates and drug control laboratories.

The Pharmaceutical Inspection Convention (PIC) has published a document (*3*), with the objective of adapting the standards of the International Organization for Standardization (ISO) of the 9000 series and related norms (*4–8*) to the activities of the GMP inspectorates of Member States. It is based on European Standard EN 45012, *General criteria for certification bodies operating quality systems certification* (*9*), but has been modified for this particular purpose.

1. Introduction

These requirements are applicable to quality systems for the operation of inspection services within competent authorities concerned with GMP inspections. It is intended that each inspection service should use these requirements as the basis for developing its own quality system.

The establishment and operation of a quality system is an essential element in the mutual recognition of national GMP inspections. The willingness to accept national inspections is significantly enhanced when it is known that the GMP inspectorate of the competent authority follows uniform procedures incorporating quality system principles. The quality system should include all the activities involved in the inspection.

2. Glossary

authorized person
A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale (*10*).

quality audit
An examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (*2*).

quality manual
A handbook that describes the various elements of the system for assuring the quality of the test results generated by a laboratory (see section 11).

quality system
An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality (*2*).

standard operating procedure (SOP)
An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation (*2*).

3. Administrative structure

3.1 The structure, membership and operation of the GMP inspectorate should be such that impartiality is safeguarded.

3.2 The national inspection services are responsible for ensuring that the requirements of the relevant national legislation are satisfied.

3.3 All personnel employed or used by the GMP inspectorate, including outside inspectors or subcontracted personnel, should not be subject to any commercial, financial or other pressures which might affect their judgement. They should not be under the control of pharmaceutical manufacturers, and must be assessed and licensed.

3.4 The system for obtaining fees should not improperly influence the inspection procedure.

Recommended procedure

The administrative structure, membership, operation and legal status of the GMP inspectorate should be described in the quality manual (see section 11).

The quality manual should show how all personnel working for the GMP inspectorate, including subcontracted staff or advisers, and persons serving on committees providing advice, can maintain their impartiality. The GMP inspectorate should ensure that such persons:

(a) are not subject to any commercial, financial or other pressures which might influence their judgement;

(b) are not improperly influenced in their inspection of pharmaceutical manufacturers or persons assessed;

(c) have not been involved in the design or maintenance of inspected facilities by way of any consultancy service or commercial arrangement.

The remuneration of GMP inspectorate personnel engaged in inspection activities should not depend on the result of such activities or on the granting of a marketing authorization.

Only in exceptional cases may GMP inspectorates provide advisory or consultancy services. Where the GMP inspectorate does provide such services, it should develop a code of conduct or defined policy which clearly distinguishes between the process of inspection and that of providing an advisory or consultancy service to clients. This service should be of benefit to all of industry, and not solely to individual manufacturers.

4. Terms of reference

4.1 The functions of the GMP inspectorate should be clearly defined and should cover:

(a) legal responsibilities;

(b) the formulation of policies;

(c) an overview of the implementation of its policies;

(d) an overview of its finances;

(e) as required, the setting-up of committees to which defined activities are delegated.

Recommended procedure

The terms of reference, legal responsibilities and functions of the GMP inspectorate and the way in which policy guidelines are established should be documented in the quality manual.

For any committee established to advise the GMP inspectorate or the chief inspector, the following details should be included:

(a) its role and function;

(b) the procedure for selecting and appointing the members (the names of the chairperson, secretary and members, their current appointments and the interests, if any, which they represent on the committee, should be available);

(c) the rules of procedure.

5. Organizational structure

5.1 The GMP inspectorate should have an organization that enables it to maintain the capability to perform its technical functions satisfactorily.

5.2 The GMP inspectorate should have:

(a) documentation clearly identifying its legal status;

(b) an organizational chart showing clearly the responsibility and reporting structure of the inspectorate and, in particular, the relationship between its inspection and authorization (licensing) functions;

(c) a description of the means by which the inspectorate obtains financial support;

(d) a description of the relationship between the GMP inspectorate and other departments within the drug regulatory authority and other government agencies, where they operate as separate bodies.

5.3 The GMP inspectorate should have and make available a formal statement explaining how the results of inspections are taken into account in granting and maintaining authorizations (licences).

5.4 The senior management of the GMP inspectorate should make a formal commitment to the recommended principles by ensuring that the quality policy of the inspectorate is documented, relevant to the objectives, and implemented.

5.5 The responsibility, authority and reporting structure of the GMP inspectorate should be clearly defined and documented (see above) and should be supported by written job descriptions for each member of staff.

5.6 An appropriately experienced, responsible and qualified person (*2*) should be nominated to carry out the quality assurance function, including implementing and maintaining the quality system. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.

5.7 The GMP inspectorate should have sufficient resources at all levels to enable it to attain its objectives effectively and efficiently. Senior management should ensure that all personnel are competent to carry out their assigned duties. They should receive appropriate training that should be documented and its effectiveness assessed.

5.8 Periodic management reviews of the quality system should be conducted and documented; records of these reviews should be retained for a specified period of time.

Recommended procedure

The above-mentioned recommendations are intended to ensure a reasonable level of transparency, both nationally and internationally.

The organizational chart, source(s) of finance, legal status of the GMP inspectorate and its relationship with the drug regulatory authority and other government agencies should be documented in the quality manual, together with a description of the quality system.

6. Inspection personnel

6.1 The personnel of the GMP inspectorate should be competent to perform the functions that they undertake.

6.2 The GMP inspectorate should maintain information on the relevant qualifications, training and experience of each inspector. Records of training and experience should be kept up to date.

6.3 Personnel should have clear, documented instructions specifying their duties and responsibilities. These instructions should be kept up to date.

6.4 When work is subcontracted to an external body or use is made of experts, the inspectorate should ensure that the personnel employed meet the relevant requirements of the quality system. The liability of third party inspectors should be clearly defined in the contract or agreement.

6.5 The GMP inspectorate should possess the required personnel, expertise and other resources to perform inspections of manufacturers and wholesale distributors to determine whether they comply with the principles and guidelines of current good practices and with the relevant legislation.

6.6 The staff responsible for inspections should have appropriate qualifications, training, experience and knowledge of the inspection process. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of good practices and the relevant legislation and be able to make an appropriate risk assessment. Knowledge of current technology is essential, including computerized systems and information technology.

6.7 The GMP inspectorate should establish a documented system for recruiting and training its personnel. The training received and the training needs of each member of staff should be regularly reviewed, and individual training records should be maintained.

Recommended procedure

The credibility of the GMP inspection process will depend to a large degree on the technical competence and integrity of the inspectors. The quality manual should provide up-to-date details of the names,

qualifications, experience and terms of reference (job description and duties to be performed) of each member of staff engaged in the GMP inspection process (see also section 10).

Formal arrangements should exist for personnel training, and details of these arrangements should be documented. Training undertaken by each member of staff engaged in GMP inspections should be documented (see also "Recommended procedure" in section 10).

A documented procedure for selecting the members of an inspection team and deciding on its size should be available. The inspection team may include a person or persons with specialist knowledge and/or experience of a particular area of technology.

If an inspection is carried out on behalf of the GMP inspectorate by an external body or person, the GMP inspectorate should ensure that the external personnel satisfy the relevant requirements contained in these recommendations.

GMP inspectors working with or advising the GMP inspectorate should:

(a) be academically qualified in a recognized scientific/technological discipline related to pharmaceuticals (normally pharmacy, chemistry or microbiology); direct personal experience of pharmaceutical manufacture or control is not a requirement but would be considered as a valuable asset for an inspector;

(b) have satisfactorily completed a recognized training course on auditing quality management systems;

(c) undergo at least 10 days of training per year (e.g. courses, symposia, conferences, etc.);

(d) have a competent working knowledge of the WHO guidelines on GMP for pharmaceutical products (*2*) and/or the GMP inspection procedures of the relevant national regulatory authority;

(e) have undergone appropriate training in the current procedures and techniques of GMP inspections before conducting an inspection alone;

(f) have the necessary personal qualities of integrity, tact and character to perform the duties of a GMP inspector.

7. Documentation

7.1 The GMP inspectorate should maintain a system for the control of all documentation relating to GMP inspections of manufacturers and recommendations relating to authorization holders, and should ensure that:

(a) the current versions of the appropriate documentation are available at all relevant locations;

(b) all revised documents or amendments to documents are correctly authorized and processed in a manner which ensures that they are introduced without delay;

(c) superseded documents are removed from use throughout the GMP inspectorate and elsewhere in the organization and its agencies, but are retained for a defined period of time.

7.2 The GMP inspectorate should ensure that all of its activities are described in SOPs that clearly describe the responsibilities, policy and actions. These should include, but not be limited to, training (introduction, GMP and task-related), inspections, reporting after inspections, handling of complaints, licensing (issue, suspension, revocation), certification, documentation control, planning and handling of appeals.

7.3 Proper and accessible records should be maintained of the activities carried out, including training, as well as the assessment of inspectors after training, the preparation of inspection reports, the handling of complaints, and the drawing-up of authorized checklists (where in use) and other related documents.

7.4 Reports should be prepared on all inspections performed. They should be prepared in the approved format, and signed and dated by the relevant inspector.

7.5 The documentation system should ensure that any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents.

Recommended procedure

The following information should be included or referred to in the quality manual:

(a) a list of all the documents used;

(b) for each document, the name(s) or position(s) of the person(s) responsible for authorizing its issue and any subsequent amendments or changes;

(c) a description of the system whereby relevant documents and subsequent amendments are made available at the appropriate location from the point of view of the functioning of the inspection process;

(d) the method by which amendments and changes are made, so that documents are speedily updated, changes recorded and superseded documents promptly withdrawn and archived.

8. Records

8.1 The GMP inspectorate should maintain a system of records to suit its particular method of operation and circumstances. It must comply with the relevant obligations under national legislation and demonstrate that the quality system is operating satisfactorily.

8.2 Records should be available which demonstrate that all the relevant procedures have been followed in the performance of each GMP inspection, including the initial inspection, the recommendation for issue of a marketing authorization, routine inspections and corrective action.

8.3 All records should be safely stored for an adequate period, and held under conditions that guarantee their security and confidentiality, unless otherwise required by the national legislation.

Recommended procedure

The quality manual should describe or refer to separate SOPs which describe the system adopted by the GMP inspectorate for maintaining its records. The manual should include blank specimen copies of the various checklists, certificates and reports used during the inspection process and describe the way in which these are processed, stored and archived, and/or disposed of.

The procedures for recommending to the authorization holder the issue, suspension or revocation of marketing authorizations should be described.

Documented staff instructions on security and on the use and handling of inspection reports should be identified and described in accordance with the confidentiality requirements specified in national legislation. Information as to who should have access to confidential information should be given and such access should be controlled.

Records associated with inspection activities should be retained for a minimum period of three full inspection cycles or for 6 years, whichever is the longer.

9. Inspection procedures

9.1 The GMP inspectorate should have the required resources (financial, human, facilities and others) and documented procedures to enable the inspection of manufacturing operations to be carried out

in accordance with the requirements of the WHO guidelines on GMP (*2*) and/or the national GMP guidelines.

9.2 The GMP inspectorate should require the manufacturer to have documented procedures in accordance with a quality management system, and complying with the WHO guidelines on GMP (*2*) and/or the national GMP guidelines.

9.3 The GMP inspectorate should perform regular inspections of the manufacturing premises, procedures and quality systems of authorization holders at least once every 2 years in accordance with a written inspection programme. Written inspection reports should be prepared and sent to the national regulatory authority to keep it informed of the outcome of such inspections.

9.4 The planning of inspections of manufacturers and the assessment of compliance with the planning regarding the performance of the different types of inspections should be documented. The types of inspections should include as a minimum routine inspections, specific inspections, follow-up inspections and concise inspections.

9.5 The activity of the GMP inspectorate should be described, indicating how it relates to the system(s) for granting manufacturers' and product authorizations.

9.6 The activities relating to post-marketing surveillance and product testing should be described. The description should also cover the process of handling non-conforming products (e.g. substandard or counterfeit products).

9.7 The procedure for operations in support of a surveillance sampling programme should be documented.

9.8 The GMP inspectorate should have the documented procedures and resources to enable the inspection of manufacturing and wholesale distribution operations to be carried out in accordance with the official guidelines and national legislation. A formal inspection plan should be followed. All instructions, standards or written procedures, worksheets, checklists and reference data relevant to the work of the GMP inspectorate should be kept up to date and be readily available to staff.

9.9 A chief inspector should be appointed to coordinate inspection activities if more than one inspector is involved in an inspection. The lead inspector, who should be selected by all the participating inspectors, should normally prepare the inspection report.

9.10 Observations and/or data obtained in the course of inspections should be recorded in a timely manner to prevent loss of relevant information.

9.11 Completed inspections should be reviewed to ensure that the requirements have been met.

Recommended procedure

The procedures covering initial inspections of new applicants for marketing authorizations and ongoing inspections of authorization holders should be documented.

Manufacturers should be inspected at least every 1 or 2 years, although new authorization holders should be inspected more frequently until inspectors are confident that the manufacturers are complying with the WHO guidelines on GMP and/or the national GMP guidelines. The frequency of inspection should not normally fall below once every 2 years as lack of continuity may give rise to a reduced awareness of current GMP or allow significant deficiencies to develop.

The time available for undertaking inspections should be adequate to enable sufficient investigations and enquiries to be made to give confidence in the findings of the inspection.

The report to the authorization holders following GMP inspections should include as a minimum:

(a) the name and location of the manufacturing site(s);

(b) the date(s) of the inspection(s);

(c) the reason for the inspection and the product categories and manufacturing areas inspected;

(d) the suitability of key personnel, including the authorized person;

(e) observations, failures to comply with the WHO guidelines on GMP and/or the national GMP guidelines, and the recommended frequency of reinspection;

(f) a recommendation on the issue/continuation, suspension or revocation of the marketing authorization.

The GMP inspectorate should have the power, under the national or regional legislation or other arrangements, to require reinspection of a manufacturer's premises if there are changes in personnel, facilities, internal organization or scope of activity, or if analysis of a complaint or any other information indicates that the manufacturer is failing to comply with the requirements of the WHO guidelines on GMP and/or the national GMP guidelines, or with the conditions imposed by the marketing authorization.

10. Inspection facilities required

10.1 The inspection service should have the required facilities in terms of staff, expertise, equipment and other resources to perform inspections of manufacturers to determine compliance with the requirements of the WHO guidelines on GMP and/or the national GMP guidelines. This does not preclude the use of external resources, when necessary, provided that the requirements as described for "subcontracting" are met (see section 3.3).

10.2 If inspections are carried out on behalf of the GMP inspectorate by an external body or person, the GMP inspectorate should ensure that this body or person satisfies the requirements specified in section 3.3. A properly documented agreement covering these arrangements, including confidentiality aspects and the declaration of any conflict of interests, should be drawn up.

Recommended procedure

A sufficient number of competent personnel should support the GMP inspectorate, whether employed or contracted for the functions that they undertake.

The quality manual should describe the procedures for the management of the GMP inspectors and of the necessary records. A record should be kept for each individual employed to carry out GMP inspections (whether an employee or under contract), which should include the following information:

(a) the name;

(b) the designated area of responsibility within the declared scope of the GMP inspectorate;

(c) the educational qualifications;

(d) the professional qualifications, where relevant to the activities of the GMP inspectorate;

(e) the work experience;

(f) details of the GMP inspector training received, supported by documentary evidence of course attendance and assessment results.

Where an external body or person carries out a GMP inspection, the quality manual should describe the process adopted by the GMP inspectorate to comply with the above-mentioned requirements.

Whenever an external body or person is used to carry out any function on behalf of a GMP inspectorate, the GMP inspectorate should

have documented evidence to demonstrate that the external body or person concerned is competent to do so.

Staff members authorized to carry out audits of external bodies or persons should be identified.

Documented agreements with all external bodies or persons should be available for scrutiny.

A register of all external bodies or persons employed by the GMP inspectorate should be maintained. The register should include:

(a) the name of the external body or person;

(b) the legal status of the external body and details of any relationship with a parent company, group of companies or any other organization of which the external body or person is part, with specific reference to possible conflicts of interest;

(c) the names and qualifications of all personnel engaged in GMP inspection work for the GMP inspectorate.

11. Quality manual

11.1 The GMP inspectorate should define and document its policy and objectives for, and commitment to, quality in a quality manual. It should ensure that this policy is understood, implemented and maintained at all levels in the organization.

11.2 The information contained in the quality manual and procedures should include at least:

(a) a quality policy statement;

(b) a brief description of the legal status of the GMP inspectorate (see section 4.1(a));

(c) a code of ethics and conduct relating to GMP inspection activities;

(d) a description of the organization of the GMP inspectorate, including details of any governing board, its constitution, terms of reference and rules of procedure (see section 5.2(b));

(e) the names, qualifications, experience and terms of reference of the senior staff and other GMP inspection personnel, both internal and external (see sections 6 and 10);

(f) details of training arrangements for inspection personnel (see sections 6 and 10);

(g) an organizational chart showing the responsibility and reporting structure of the inspectorate and the allocation of functions

stemming from the person in charge of the GMP inspectorate (see section 5.2(b));

(h) details of the documented procedures for inspecting manufacturers under the WHO guidelines on GMP and/or the national GMP guidelines (see section 8);

(i) details of the documented procedures for recommendations to the authorization holder for the issue, suspension or revocation of marketing authorizations (see sections 7.2 and 8.1);

(j) a list of any subcontractors used for GMP inspections and details of the documented procedures for assessing and monitoring their competence (see section 6);

(k) details of appeals procedures (see section 14);

(l) a procedure for ensuring that complaints made to the GMP inspectorate are investigated so that any shortcomings of the authorization holders are revealed (see section 16);

(m) a list of those staff members responsible for investigating complaints and those with the authority to take remedial action (see section 16);

(n) details of internal quality audits (see section 15);

(o) details of testing of samples (see sections 9.6–9.8);

(p) the control of non-conforming products (see section 9.6).

Recommended procedure

In order to keep the quality manual brief, reference may be made to other documents and/or procedures contained in other manuals.

12. Confidentiality

12.1 The GMP inspectorate should have adequate arrangements to ensure confidentiality of the information obtained in the course of its inspection activities at all levels of its organization, including committees.

12.2 The exchange of inspection reports between countries should be described. The format and content of reports should be specified.

Recommended procedure

The quality manual should describe how the GMP inspectorate discharges its responsibility for ensuring that all communications between itself and the companies inspected are kept confidential. The following are necessary:

(a) instructions to personnel on confidentiality;

(b) a written undertaking by all personnel not to divulge to third parties any information gained about any business affairs of clients;

(c) the inclusion of provisions in all subcontracts to maintain confidentiality;

(d) provisions to ensure the physical security of all documents and records relating to inspection activities.

13. Publications

13.1 The GMP inspectorate should produce and update, as necessary, a list of authorization holders, together with an outline of the scope of the marketing authorization issued to each manufacturer. The extent to which this list will be distributed should be specified.

13.2 An outline of the inspection and marketing authorization system should be available in published form.

13.3 Other publications, such as GMP guidelines and other guidelines and information brochures, should be available to industry and other interested parties, as appropriate.

Recommended procedure

The quality manual should list the publications issued by the authorization holder and GMP inspectorate. The following information should also be provided:

(a) the name of the person responsible for compiling and updating each publication;

(b) the frequency with which each publication is updated;

(c) how the publications are distributed and to whom;

(d) the procedure for issuing amendments.

14. Appeals

14.1 The GMP inspectorate should have procedures for the consideration of appeals against its decisions.

Recommended procedure

Appeals procedures should be established by the GMP inspectorate and should include:

(a) the method by which an appeal may be lodged;

(b) the method by which an impartial appeals panel, independent of the activity under review, is selected;

(c) the names and positions of the members of the GMP inspectorate to whom appeals are referred, and the procedure for handling them;

(d) a register of all appeals and their outcome.

15. Internal audit and periodic review

15.1 The GMP inspectorate should implement a system of planned and documented internal audits and periodic reviews of its compliance with the criteria of these guidelines.

15.2 There should be procedures for corrective and preventive action whenever faults are detected in the quality system, or in the performance of inspections and the general performance of the inspection service.

15.3 The management of the inspectorate should periodically review the quality system for its continuing suitability and effectiveness.

15.4 Inspectors should be evaluated before being allowed to perform inspections. Periodic reviews should also be undertaken to examine the performance of individual inspectors in order to ensure consistency among them, and in the operations and procedures of the GMP inspectorate.

15.5 A record of all audits and reviews should be kept and should include the findings, conclusions, recommendations and follow-up action. These records should be retained for a specified period of time.

Recommended procedure

Internal periodic review procedures should be documented. The review procedure should include internal audits by staff competent to ensure that all formulated procedures are adhered to. Based on the results of these audits, management must ensure that the GMP inspection system remains effective and that inspections conducted by different inspectors arrive at similar conclusions when the same operation is inspected under the same conditions.

Internal audit procedures should state:

(a) the names or positions of staff members authorized to conduct internal audits;

(b) what is to be examined and how often (a schedule for the examination of the whole organization over a given period should be drawn up);

(c) how the audit will be conducted;

(d) to whom the results will be reported;

(e) who will initiate any corrective action.

Management reviews should take account of the results of internal audits and should include:

(a) consideration of the overall operation of the GMP inspectorate;

(b) uncovering defects or irregularities in the operation of the GMP inspection system;

(c) ensuring that action has been taken to effectively correct defects revealed in previous reviews and audits.

Periodic audit by an experienced person or persons from another national regulatory authority is a useful means of providing an independent review of the GMP inspectorate's operations and procedures.

16. Complaints

16.1 The GMP inspectorate should have documented procedures for dealing with complaints arising from its activities.

16.2 A record should be maintained of all complaints received and the actions taken by the GMP inspectorate. These records should be retained for a specified period of time.

Recommended procedure

The GMP inspectorate should require each authorization holder to keep a record of all complaints received, as well as remedial actions relating to the manufacturing activities and products covered by the marketing authorization.

The GMP inspectorate should have a procedure for recording and investigating complaints received about its inspection activities. The procedure should include a list of those staff members responsible for investigating complaints and those with the authority to take remedial action.

17. Recalls

17.1 The GMP inspectorate should have a documented procedure for dealing with recalls and withdrawals of products from the market.

17.2 Records should be maintained of all recalls and withdrawals registered and dealt with by the inspectorate.

References

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3. *Recommendations on quality system requirements for GMP inspectorates of PIC Contracting States*. Geneva, Pharmaceutical Inspection Convention, 1994 (unpublished document PH/7/94; available from EFTA Secretariat, 9–11 rue de Varembé, 1211 Geneva 20, Switzerland).
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10. Good manufacturing practices: authorized person — role, functions and training. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 4 (WHO Technical Report Series, No. 885).

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Annex 9
Guidelines on packaging for pharmaceutical products

Introductory note

This review of the various elements of the packaging of a pharmaceutical product is aimed at ensuring that medicines arrive safely in the hands of the patients for whom they are prescribed.

In the manufacture of pharmaceutical products, quality assurance is defined as "the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use" (*1*).

In addition, the system of quality assurance for the manufacture of pharmaceutical products should ensure that "arrangements are made for the manufacture, supply and use of the correct starting and packaging materials" (*1*).

Public opinion sometimes considers packaging to be superfluous. However, it must be emphasized that packaging preserves the stability and quality of medicinal products and protects them against all forms of spoilage and tampering.

All medicinal products need to be protected and "consequently need to be packaged in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. . . . However, the limits of acceptability in these various respects depend, at least in part, on climatic variables. Recommendations in *The international pharmacopoeia* can only be advisory; precise quantitative standards will have to be locally determined" (*2*).

The complexity of packaging materials and the highly technological nature of medicinal products is such that manufacturers are confronted with significant problems. Interaction between packaging and such products is possible due to the combination of a multiplicity of container components and active pharmaceutical ingredients, excipients and solvents used in a variety of dosage forms.

The quality of the packaging of pharmaceutical products plays a very important role in the quality of such products. It must:

— protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen and temperature variations;
— protect against biological contamination;
— protect against physical damage;
— carry the correct information and identification of the product.

The kind of packaging and the materials used must be chosen in such a way that:

— the packaging itself does not have an adverse effect on the product (e.g. through chemical reactions, leaching of packaging materials or absorption);
— the product does not have an adverse effect on the packaging, changing its properties or affecting its protective function.

The resulting requirements must be met throughout the whole of the intended shelf-life of the product. Given the link between the quality of a pharmaceutical product and the quality of its packaging, pharmaceutical packaging materials and systems must be subject, in principle, to the same quality assurance requirements as pharmaceutical products.

The appropriate system of quality assurance for the manufacture of pharmaceutical products should therefore follow the WHO guidelines for good manufacturing practices (GMP) (*1*).

The requirements to be met by pharmaceutical packaging and packaging materials as described in compendia (pharmacopoeias) and standards (e.g. those of the International Organization for Standardization (ISO)) must be considered only as general in character. The suitability of packaging or packaging material for any particular requirements and conditions can only be ascertained through detailed packaging and stability studies on the product concerned.

Glossary

The definitions given below apply specifically to the terms used in these guidelines. They may have different meanings in other contexts.

General

bulk product

Any product that has completed all the processing stages up to, but not including, final packaging (*1*).

containers

A container for pharmaceutical use is an article which holds or is intended to contain and protect a drug and is or may be in direct contact with it. The closure is a part of the container. The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality. The following terms include general requirements for the permeability of containers (*3*):

- *Well-closed containers* must protect the contents from extraneous matter or from loss of the substance under normal conditions of handling, shipment or storage.
- *Tightly closed containers* must protect the contents from extraneous matter, from loss of the substance, and from efflorescence, deliquescence or evaporation under normal conditions of handling, shipment or storage. If the container is intended to be opened on several occasions, it must be designed to be airtight after reclosure.
- *Hermetically closed containers* must protect the contents from extraneous matter and from loss of the substance, and be impervious to air or any other gas under normal conditions of handling, shipment or storage.

Substances and dosage forms requiring protection from light should be maintained in a *light-resistant container* that — either by reason of the inherent properties of the material of which it is composed, or because a special coating has been applied to it — shields the contents from the effects of light. Alternatively, the container may be placed inside a suitable light-resistant (opaque) covering and/or stored in a dark place (*3*).

labels

All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;

(b) a list of the active ingredients (if applicable, with the International Nonproprietary Names (INNs)), showing the amount of

each present, and a statement of the net contents, e.g. number of dosage units, mass or volume;

(c) the batch number assigned by the manufacturer;

(d) the expiry date in an uncoded form;

(e) any special storage conditions or handling precautions that may be necessary;

(f) the directions for use, and any warnings and precautions that may be necessary;

(g) the name and address of the manufacturer or the company or person responsible for placing the product on the market.

marketing authorization (product licence, registration certificate)
A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, information given on the label, product information and shelf-life (*1*).

materials
A term used to denote starting materials, process aids, intermediates, active pharmaceutical ingredients, packaging and labelling materials.

packaging material
Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Primary packaging materials are those that are in direct contact with the product (*1*).

packaging process
All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product (*1*).

production
All operations involved in the preparation of a pharmaceutical product, from receipt of the starting materials, through processing and packaging, to completion of the finished product (*1*).

quarantine
The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing (*1*).

Containers for pharmaceuticals[1]

ampoule
A container sealed by fusion and to be opened exclusively by breaking. The contents are intended for use on one occasion only.

bag
A container consisting of surfaces, whether or not with a flat bottom, made of flexible material, closed at the bottom and at the sides by sealing; the top may be closed by fusion of the material, depending on the intended use.

blister
A multi-dose container consisting of two layers, of which one is shaped to contain the individual doses. Strips are excluded.

bottle
A container with a more or less pronounced neck and usually a flat bottom.

cartridge
A container, usually cylindrical, suitable for liquid or solid pharmaceutical dosage forms; generally for use in a specially designed apparatus (e.g. a prefilled syringe).

gas cylinder
A container, usually cylindrical, suitable for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

injection needle
A hollow needle with a locking device intended for the administration of liquid pharmaceutical dosage forms.

injection syringe
A cylindrical device with a cannula-like nozzle, with or without a fixed needle and a movable piston, used for the administration, usually parenteral, of an accurately measured quantity of a liquid pharmaceutical form. The syringe may be prefilled, and can be for single-dose or multi-dose use.

[1] Based on a list of terms drawn up in response to a request from the European Commission to revise and replace the guidelines of the Committee for Proprietary Medicinal Preparations (III/3593/91).

pressurized container
A container suitable for compressed, liquefied or dissolved gas fitted with a device that, after its actuation, produces a controlled spontaneous release of the contents at atmospheric pressure and room temperature.

single-dose container
A container for single doses of solid, semi-solid or liquid preparations.

strip
A multi-dose container consisting of two layers, usually provided with perforations, suitable for containing single doses of solid or semi-solid preparations. Blisters are excluded.

tube
A container for multi-dose semi-solid pharmaceutical forms consisting of collapsible material; the contents are released via a nozzle by squeezing the package.

vial
A small container for parenteral medicinal products, with a stopper and overseal; the contents are removed after piercing the stopper. Both single-dose and multi-dose types exist.

1. Aspects of packaging

1.1 *General considerations*

Packaging may be defined as the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use.

The aspects of packaging to be considered (*4*) include:

— the functions of packaging;
— the selection of a packaging material;
— the testing of the material selected;
— filling and assembling;
— sterilization;
— storage and stability.

Packaging materials (see section 2) include printed material employed in the packaging of a pharmaceutical product, but not any outer packaging used for transportation or shipment. Examples of the types of materials used are shown in Table 1.

A distinction must be made between primary and secondary packaging components. The primary packaging components (e.g. bottles,

Table 1
Types of raw materials used in packaging

Types of materials	Uses
Cardboard	Boxes Display units
Paper	Labels Leaflets
Glass	Ampoules Bottles Vials Syringes Cartridges
Plastic	Closures Bottles Bags Tubes Laminates with paper or foil
Metal, e.g. aluminium	Collapsible tubes Rigid cans Foils Needles Gas cylinders Pressurized containers
Rubber	Closures, including plungers

vials, closures, blisters) are in direct physical contact with the product, whereas the secondary components are not (e.g. aluminium caps, cardboard boxes). The choice of primary and/or secondary packaging materials will depend on the degree of protection required, compatibility with the contents, the filling method and cost, but also the presentation for over-the-counter (OTC) drugs and the convenience of the packaging for the user (e.g. size, weight, method of opening/reclosing (if appropriate), legibility of printing).

Containers may be referred to as primary or secondary, depending on whether they are for immediate use after production of the finished product or not. Both single-dose and multi-dose containers exist. Containers may be well-closed, tightly closed, hermetically closed or light-resistant, as defined in the glossary (*3*).

The packaging process, as defined in the glossary, is the process that a bulk material must undergo to become a finished product. The properties and attributes of the product should be as specified by the manufacturer and required by the user. The packaging process consists of the following stages:

— filling and assembling;
— sterilization in the final container, if applicable;
— placing labels on the container;
— storage at the manufacturing and shipping sites.

Packaging documentation (*1*) includes aspects related to:

— specifications and quality control, including batch records;
— labels, inks and adhesive materials (e.g. glue);
— package inserts for patients.

Apart from primary and secondary packaging, two types of special packaging are currently in use, as follows:

- *Unit-dose packaging*. This packaging guarantees safer medication by reducing medication errors; it is also more practical for the patient. It may be very useful in improving compliance with treatment and may also be useful for less stable products.
- *"Device" packaging*. Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration by means of devices such as prefilled syringes, droppers, transdermal delivery systems, pumps and aerosol sprays. Such devices ensure that the medicinal product is administered correctly and in the right amount.

1.2 *Functions of packaging*

1.2.1 *Containment*

The containment of the product is the most fundamental function of packaging for medicinal products. The design of high-quality packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging:

— not to leak, nor allow diffusion and permeation of the product;
— to be strong enough to hold the contents when subjected to normal handling;
— not to be altered by the ingredients of the formulation in its final dosage form.

1.2.2 *Protection*

The packaging must protect the product against all adverse external influences that may affect its quality or potency, such as:

— light
— moisture
— oxygen
— biological contamination
— mechanical damage.

The compatibility of the packaging with the active pharmaceutical ingredients is very important in maintaining the integrity of the product.

Stability. Information on stability is given in the guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms (*4*).

For primary packaging, it is necessary to know the possible interactions between the container and the contents. Normally, product/component stability and compatibility are confirmed during the primary research and development stage.

While excluding the effect of external factors on the product, the packaging itself should not interact with it so as to introduce unacceptable changes. There are numerous possibilities of interactions between (primary) packaging materials and pharmaceutical products, such as:

— the release of chemicals from components of the packaging materials;
— the release of visible and/or subvisible particles;
— the absorption or adsorption of pharmaceutical components by the packaging materials;
— chemical reactions between the pharmaceutical product and the packaging materials;
— the degradation of packaging components in contact with the pharmaceutical products;
— the influence of the manufacturing process (e.g. sterilization) on the container.

The active pharmaceutical ingredients should remain within their specification limits over the shelf-life of the pharmaceutical product. The question of whether a packaging will provide the required protection for the pharmaceutical product and the required stability over a certain time period can only be answered by means of real-time stability studies. Such studies must evaluate the changes in the quality of the product, in contact with its packaging, during a period equivalent to its intended shelf-life.

In addition, packaging must meet the following requirements:

— it must preserve the physical properties of all dosage forms and protect them against damage or breakage;
— it must not alter the identity of the product;
— it must preserve the characteristic properties of the product, so that the latter complies with its specifications;

— it must protect the product against undesirable or adulterating chemical, biological or physical entities.

Storage. Packaging materials should be stored in accordance with GMP for storage areas (*1*; see Appendix 1). The characteristics of the active pharmaceutical ingredients will determine whether different packaging will be needed. For example, the packaging requirements of medicinal products kept at temperatures between 2 and 8 °C may differ from those of products intended for tropical countries or light-sensitive products. If the contents are sterile, sterility must be maintained, including that of any unused remaining product.

The shelf-life and utilization period are always determined in relation to storage conditions and the stability of the active pharmaceutical ingredient.

Normal storage conditions are defined as "storage in dry, well-ventilated premises at temperatures of 15–25 °C or, depending on climatic conditions, up to 30 °C. Extraneous odours, other indications of contamination, and intense light have to be excluded" (*5*).

1.3 *Presentation and information*

Packaging is also an essential source of information on medicinal products. Such information is provided by labels and package inserts for patients.

The information provided to the patient may include the following:

— the name of the patient;
— the identification number for dispensing records;
— the name, strength, quantity and physical description or identification of the medicinal product;
— directions for use and cautionary statements, if applicable;
— the storage instructions;
— the date of dispensing and period of use (related to the expiry date);
— the name and address of the dispenser.

1.3.1 *Labels*

Throughout manufacturing, a succession of specific outer labels are applied to the container of the medicinal product. The level of processing is indicated by the following words:

— quarantine
— storage
— distribution.

Specifications for labels for finished drug products are defined in the WHO guidelines on GMP for pharmaceutical products (*1*; see Appendix 2).

Written labels on the packaging:

- Permit the identification of each active ingredient by means of its INN, and also give the dosage form and the trade name/trademark. All information concerning the medicinal product, as required by national legislation, must be stated on the packaging.
- Preserve the stability of the medicinal product by giving advice on its storage (*4*):

  > After the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:
  >
  > — store under normal storage conditions;
  > — store between 2 and 8 °C (under refrigeration, no freezing);
  > — store below 8 °C (under refrigeration);
  > — store between –5 and –20 °C (in a freezer);
  > — store below –18 °C (in a deep freezer).

- Permit the follow-up of a specific medicinal product by means of the batch number on the labels. It must be possible to follow the route of distribution of a product from the manufacturing process to its administration to the patient with the aim of locating and identifying products that are of potential risk (e.g. blood products, blood-derived products).
- Mask the real identity of the medicinal product in clinical studies. This is extremely important in clinical trials in determining the real efficacy of a medicinal product in blinded studies. If the identity is masked by a code, it must be possible to disclose it at any time in a medical emergency.

National legislation must be followed with regard to the information provided to the patient, as well as the record-keeping and packaging instructions.

1.3.2 *Repacking, relabelling and dispensing*

In some countries, it is common practice not to dispense drugs in the original packaging, but rather in a personalized manner to each patient. This applies especially to solid oral dosage forms, and involves the "repacking" and "relabelling" of drugs in small quantities. Different drugs may even be included in "customized" medication packages, also referred to as "patient med packs". The quantities of drugs supplied in this way are usually enough only for a short period of time,

i.e. to provide drugs for immediate use. It should be remembered, however, that data obtained in stability studies undertaken by the manufacturer are no longer valid for drugs removed from the original package.

Where repacking and relabelling are necessary, the WHO guidelines on GMP for pharmaceutical products (*1*) should be followed to avoid any mix-up or contamination of the product, which could place the patients' safety at risk.

1.3.3 *Package inserts for patients (patient information leaflets)*

Product information must help patients and other users to understand the medication. The patient package insert, together with the label, provides the patient with key information concerning the proper use of the product, potential adverse drug reactions and interactions, storage conditions and the expiry date.

In OTC medicinal products, the package insert, together with the label, may constitute the only pharmaceutical advice that the patient receives.

1.4 ***Compliance***

Packaging and labelling may help to reinforce the instructions given by the physician or the pharmacist, and improve compliance with drug therapy. In this respect, packaging becomes a compliance aid.

The design of pharmaceutical packaging should be such that the product can easily be administered in a safe manner to the patient. If the patient feels at ease with the packaging and route of administration, the design of the packaging may become a key factor in increasing compliance. This is also an important factor in clinical trials.

1.5 ***Protection of patients***

Packaging must not only increase compliance through its design, but must also protect the patient and indicate the integrity of the product. Packaging equipped with a tamper-evident device protects against incidental and accidental poisoning. To protect children, several child-resistant closures have been developed (see section 2.2.3).

1.6 ***Detection of counterfeiting***

The Forty-first World Health Assembly, after reviewing the report of the Executive Board on the implementation of WHO's revised drug strategy, requested: ". . . governments and pharmaceutical manufacturers to cooperate in the detection and prevention of the increasing

incidence of the export or smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations" (*6*).

Several documents (*2*, *6–9*) show that counterfeit pharmaceutical products are in wide circulation. In November 1985, during the WHO Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, concern was expressed regarding the extent to which counterfeit pharmaceutical products were in circulation in developing countries (*10*). In view of the importance of this issue, a text has been drafted to provide model provisions to deal with counterfeit drugs (*11*).

The design of the packaging must therefore contribute to preventing tampering with, or the counterfeiting of, certain medicinal products. Such tamper-evident containers can allow the visual inspection of the medicinal product before use, and this may serve as a first stage in detecting counterfeit drugs.

2. Packaging materials and closures

In accordance with the methods of use and administration of medicinal products, packaging materials, closures and containers vary a great deal and have to meet a wide variety of different requirements. All the routes used for systemic access have demanding requirements, which often can only be met by complex structured and formulated medicinal products. This is particularly true of the new medicinal products that are now appearing, such as those administered via transdermal delivery systems.

To ensure the efficacy of a product during its total shelf-life, pharmaceuticals must be regarded as a combination of the medicinal product itself and the packaging.

2.1 *Types of material*

Only the most commonly used packaging materials and containers are described here.

2.1.1 *Glass*

For a large number of pharmaceuticals, including medicinal products for oral and local administration, glass containers are usually the first choice (e.g. bottles for tablets, injection syringes for unit- or multi-dose administration). Different types of glass may be necessary, depending on the characteristics and the intended use of the medicinal products concerned.

Manufacturers should arrange with their suppliers to obtain the appropriate type of glass container for the intended use. Suppliers

should provide the raw and packaging materials in conformity with industrial norms. Classifications of types of glass are given in the European and United States pharmacopoeias, whereas no such classification exists in the Japanese pharmacopoeia.

Glass can be tested for light transmission and hydrolytic resistance. In the Japanese pharmacopoeia, such tests are described only for glass containers for injection, whereas in the European and United States pharmacopoeias they are given for all types of glass containers.

2.1.2 *Plastics*

Some containers are now being made of plastics; the main use is for bags for parenteral solutions. Plastic containers have several advantages compared with glass containers:

— they are unbreakable
— they are collapsible
— they are light.

The European, Japanese and United States pharmacopoeias all describe materials of the same type, but there are considerable differences in the classification and presentation.

As far as tests are concerned, the three pharmacopoeias are extremely difficult to compare. The European pharmacopoeia is the most detailed and requires tests in relation to the use and routes of administration of the medicinal product. Moreover, the same concept is extended to bulk containers for active ingredients.

2.1.3 *Metal*

Metal containers are used solely for medicinal products for non-parenteral administration. They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders. Aluminium and stainless steel are the metals of choice for both primary and secondary packaging for medicinal products. They have certain advantages and provide excellent tamper-evident containers.

Since metal is strong, impermeable to gases and shatterproof, it is the ideal packaging material for pressurized containers.

Descriptions and tests can be found in the norms and standards of the ISO; these have been established in collaboration with manufacturers. Requirements are not given in pharmacopoeias; the suitability of a particular material for a container is normally established by conducting stability studies in which the material is in contact with the drug in question.

2.2 *Closures*

Closures used for the purpose of covering drug containers after the filling process should be as inert as possible. They should not give rise to undesired interactions between the contents and the outside environment, and should provide a complete seal. Besides their protective function, closures must also allow the easy and safe administration of the drug.

Depending on the application, closures may have to be pierced with a needle for intravenous sets. Such closures are made from elastomeric materials (rubbers), while those that cannot be pierced are generally made from plastics such as polyethylene or polypropylene.

Depending on the type of container, closures may have different shapes and sizes, e.g. stoppers for infusion or injection bottles or plungers for prefilled syringes. A special design of stopper may also be required for some pharmaceutical production processes such as lyophilization.

Closures, as primary packaging components, are of critical importance and must be carefully selected. They are an essential component of the container and, as such, an integral part of the drug preparation.

A container type which does not require a removable closure at the time of administration is usually preferred since such a container/closure system avoids, or at least minimizes, the risk of biological and other contamination as well as tampering.

For parenteral preparations, the combination of glass containers and elastomeric closures, usually secured by an aluminium cap, is widely used. Typical examples are infusion bottles, injection vials and prefilled syringes. The rubber closures used within such a system must be carefully selected in accordance with the intended purpose. Most often, improper rubber closures are the cause of incompatibility between the packaging and the drug.

2.2.1 *Rubber closures*

Rubber consists of several ingredients, one of which is elastomer. Modern rubber compounds used in packaging pharmaceuticals contain only a limited number of ingredients, which are very difficult to extract. Closures made from such materials generally do not pose any problems, and can be used in contact with a large number of drug preparations.

Rubber closures for pharmaceutical use must meet the relevant requirements of the most important pharmacopoeias (the European,

Japanese and United States pharmacopoeias). International standards have also been established (ISO 8871). It should be emphasized that the requirements of pharmacopoeias and standards must be seen as minimal requirements. The suitability of a rubber closure for a given application can only be established by means of stability studies.

2.2.2 *Caps or overseals*

Caps or overseals are used to secure the rubber closure to the container in order to maintain the integrity of the seal under normal conditions of transport, handling and storage during the intended shelf-life of the product. Such caps are usually made of aluminium and can be equipped with a plastic top to facilitate opening. Caps also provide evidence of tampering: once opened or removed they cannot be repositioned. This is especially true for caps with a plastic top.

2.2.3 *Special types of closure*

Demographic trends are causing new problems for packaging designers. Thus while child-resistant closures safeguard children against drug intoxication, opening such packaging may prove difficult for the increasing number of elderly persons in the population.

Tamper-evident closures. Tampering includes three aspects, namely altering, pilfering and falsifying the pharmaceutical product.

To prevent tragic accidents and especially malicious tampering, manufacturers try to create safe packaging and governments continue to update regulations to include new tamper-evident technology. In 1975, the United States Food and Drug Administration issued a regulatory requirement for tamper-evident packaging to be used for ophthalmic preparations, thus ensuring that such preparations remained sterile until their use (*12*). This regulation specifies that the closures must be sealed in such a manner that the contents cannot be used without destroying the seal. In 1982, a further regulation (*13*) on tamper-evident packaging for OTC human drug products described such packaging as "having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred".

The concept of tamper-evident packaging is also found in the "General Notice" and "Requirements" of the United States pharmacopoeia, which stipulate that all OTC drugs must comply with the tamper-evident packaging and labelling requirements of the Food and Drug Administration, unless specifically exempted. Products covered by the regulation include all OTC drugs, toothpaste and topical

dermatological products, oral cosmetic liquids, contact lens solutions and tablets.

In May 1992, the Food and Drug Administration (*14*) listed 11 technologies capable of satisfying the definition of tamper-evident packaging, while a twelfth was added for sealed cartons. The list includes film wrappers, blister packs, bubble packs, heat-shrunk bands or wrappers, paper foil or plastic packs, bottles with inner mouth seals, tape seals, breakable cap-ring systems, sealed tubes or plastic blind-end heat-sealed tubes, sealed cartons, aerosol containers and all metal and composite cans.

Child-resistant closures. Tragic accidents involving the drug intoxication of children has led to new legislation making it difficult for drug packaging to be opened by young children, while allowing adults easy access. Such packaging is designated as child-resistant.

Certain protocols for child-resistant packaging were established in the USA in 1966. In 1970, the Poison-Prevention Packaging Act was passed and placed under the jurisdiction of the Food and Drug Administration. This Act was transferred in 1973 to the Consumer Product Safety Commission, which is responsible for drugs and household substances (*15*). The use of child-resistant packaging has proved effective in reducing child mortality from intoxication by oral prescription drugs, and it is now recognized worldwide that children must be protected against such intoxication.

The ISO has published an internationally agreed standard test procedure for reclosable child-resistant packaging (*16*). In Europe several norms have been introduced, which complement the ISO standard (*17*, *18*).

The European Committee for Standardization (CEN) has defined a child-resistant package as one "which makes it difficult for young children to gain access to the contents, but which is not too difficult for adults to use properly in accordance with the requirement of this European standard" (*19*).

The three most common reclosable child-resistant types of closure are the "press–turn", the "squeeze–turn" and a combination lock.

To determine whether a packaging is child-resistant, it must be subjected to the ISO test procedure for reclosable child-resistant packaging (*14*).

Most designs that are child-resistant require two hands to open the closure. Such packaging can cause problems for elderly people, and can even lead to the deliberate purchase of drugs with packaging that

is not child-resistant; alternatively, the child-resistant closure may not be replaced on the container. An optional "elderly adult test" has been inserted in the ISO standard to deal with this problem.

3. Quality assurance aspects of packaging

3.1 *General considerations*

To ensure that patients and consumers receive high-quality drugs, the quality management system must take the following considerations into account if the required quality of packaging is to be obtained:

— the requirements of the national authorities and the relevant legislation
— the product
— the production process
— the manufacturers' internal policies (safety, marketing, etc.).

Bad packaging which is the result of deficiencies in the quality assurance system for packaging can have serious consequences, and packaging defects can create problems that may result in drug recalls. Such defects may include breakage, and problems relating to printing or inks, or errors on labels and package inserts (patient information leaflets). The use of GMP and quality control will prevent the release of a defective medicinal product.

Packaging processes and equipment need validation/qualification in the same way as any other part of processing within a pharmaceutical facility.

3.2 *Quality control*

Pharmacopoeial specifications and standards for quality control established by national drug quality control laboratories, as already mentioned, can only be regarded as general in character and must be interpreted as minimum standards. The essential part of quality control is performed by the manufacturer during the development, production, release and post-marketing surveillance of the entire medicinal product, i.e. the finished dosage form in its primary and secondary packaging. As pointed out by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-second meeting (*1*):

> Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

In the production chain, quality control for packaging contains several critical points. The basic requirements for quality control are as follows (*1*):

> (a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting and testing starting materials, packaging materials, and intermediate, bulk and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
>
> (b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.
>
> (c) Test methods must be validated.
>
> (d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.
>
> (e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled.
>
> (f) Records must be made of the results of inspecting and testing materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.
>
> . . . The quality control department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in the environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

Tests and assays are normally carried out at room temperature (between 15 and 25°C, or up to 30°C in some climatic zones), unless otherwise indicated. *The international pharmacopoeia* gives alternative methods to be used if certain instruments are not available.

3.2.1 *Sampling*

Sampling is used to check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments, detecting adulteration of the medicinal product, obtaining a sample for retention, etc.

The sampling procedure must take into account the homogeneity and uniformity of the material so as to ensure that the sample is representative of the entire batch.

The sampling procedure should be described in a written protocol. Further details are given in "Sampling procedure for industrially manufactured pharmaceuticals" (*20*).

3.2.2 *Testing programme*

The testing programme for quality control purposes may vary from one manufacturer to another. Quality control tests are intended to check the identity of the material concerned. Complete pharmacopoeial or analogous testing may also be carried out, as may special tests, where necessary.

All written specifications for packaging materials and containers should include the nature, extent and frequency of routine tests. Routine tests vary according to the type of material and its immediate packaging, the use of the product, and the route of administration. Nevertheless, such tests usually include the following (*21*):

— visual inspection (cleanliness, defects)
— tests to identify the material
— dimensional tests
— physical tests
— chemical tests
— microbiological tests.

3.3 ***Inspection and audit***

Self-inspection is covered in Appendix 3, which is taken from Annex 1 of the thirty-second report of the Committee (*1*).

3.3.1 *Rules*

It is extremely important to control the security and quality of packaging. The requirements to be met by packaging for pharmaceutical products are more stringent than those for the packaging of food products, although many similarities exist. The goal of inspection is to ascertain the quality of the products, and especially the quality of the packaging. Items for self-inspection include documentation, storage of starting materials and finished products, validation of programmes, production and in-process controls, calibration of instruments or measurement systems, control of labels, sanitation and hygiene, recall procedures, premises (including personnel facilities), and maintenance of buildings and equipment.

Labels play an important part in the quality of packaging. Packaging and labelling errors in the manufacture of pharmaceutical products are often reported.

3.3.2 *Audits of suppliers*

Pharmaceutical manufacturers are usually audited or inspected by national or international licensing authorities; the same applies to suppliers of starting materials, active pharmaceutical ingredients, excipients and packaging materials. All suppliers of pharmaceuticals and packaging materials play an important role in the chain of quality assurance of the final medicinal product.

Further details can be found in the twenty-fifth and thirtieth reports of the Committee (*2*, *22*), and "General requirements for dosage forms" in *The international pharmacopoeia* (*3*).

4. Protection of the environment

The protection of the environment has become increasingly important in many countries in recent years. Greater attention has been paid to the disposal and recycling of waste, and legislation has been introduced in many countries.

4.1 ***Packaging waste***

Pharmaceutical packaging represents a very small percentage of waste, but its disposal can cause problems for the environment. For this reason, the Committee, at its thirty-second meeting (*1*), decided that:

> . . . Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separated, enclosed cupboards, as required by national legislation.
>
> . . . Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Environmental problems result from the methods used for waste disposal, and will depend on the type of packaging waste concerned. Such waste may include:

— uncontaminated waste (assimilated to domestic waste: paper, cardboard, glass, plastic);
— contaminated waste (paper, cardboard, glass, plastic), e.g. waste that has been in contact with blood, blood-derived products, radioactive products or cytotoxic products.

The method of disposal will therefore vary but should always be in accordance with national legislation. Contaminated packaging is often incinerated. The methods of disposal of uncontaminated packaging are shown in Table 2.

Table 2
Methods of disposal of uncontaminated packaging

Material	Recycling	Landfill	Incineration
Paper, cardboard	+++	++	++
Plastics	++	+	+++
Glass	+++	++	NA
Rubber	+	++	+++
Metal	+++	+	NA

+++: Highly recommended; ++: recommended; +: acceptable; NA: not applicable.

4.2 *Waste policies*

Waste is created at all stages in the production, supply and use of a pharmaceutical product. At each step, care therefore needs to be taken, either by the manufacturer or the end-user, to protect the environment.

Environmental concerns in the international community have led to certain changes in the conditions for the licensing of medicines (*23*). Thus an environmental risk assessment may have to be carried out in some cases in order to identify potential risks to the environment arising from the storage, use and disposal of medicinal products. The medicinal product as a whole may become the subject of the environmental risk assessment so that consideration has to be given not only to the active ingredient but also to the adjuvants/excipients in the formulation, and the primary and secondary packaging.

Another major environmental issue affecting certain types of pharmaceutical products concerns the chlorofluorocarbon (CFC) propellants, and the threat that they represent to the ozone layer (*24*). A European directive has been published on this subject (*25*).

In several European countries, manufacturers must dispose of their drug waste, or must pay a specialized company to do so for them, and are encouraged to salvage packaging waste. Faced with this problem, manufacturers and pharmacists have, respectively, introduced new directives and new process policies aimed at:

- *Reducing packaging.* Efforts should be made to reduce the volume and weight of packaging materials, and to eliminate packaging which is not essential for the protection of the contents of medicinal products.
- *Salvaging and recycling packaging.* The use of environmental-friendly packaging needs to be considered, i.e. recyclable or degradable packaging. (Valuable packaging materials, such as

aluminium, have been extensively recycled for many years. Recently, paper, glass and plastic materials have joined the list of recyclable packaging materials.) However, materials that have been in contact with toxic or highly potent drugs require special consideration.

- *Eliminating and incinerating packaging.* Some plastic materials cannot be recycled and are therefore incinerated. The burning of polyvinyl chloride (PVC) is controversial since, if combustion is not complete, it causes a potential increase in the levels of dioxin in the environment. Incineration can be recommended if the combustion heat produced by it can also be used for other purposes. Developing countries are often short of incinerators. This method is nevertheless regarded as the best available for the elimination of contaminated packaging.

5. Quality specifications

5.1 *Requirements in The international pharmacopoeia*

5.1.1 *Packaging materials*

Monographs for inclusion in Volume 6 of *The international pharmacopoeia* (*3*) have been proposed for glass containers and rubber closures.

5.1.2 *Requirements for dosage form containers*

Every pharmaceutical preparation must comply with the labelling requirements laid down in the WHO guidelines on GMP for pharmaceutical products (*1*).

Tablets. These should be kept in well-closed containers and protected from light, moisture, crushing and mechanical shock. Any special storage conditions should be stated on the label. Tablets should be able to withstand handling, including packaging and transportation, without losing their integrity. Moisture-sensitive forms, such as effervescent tablets, should be stored in tightly closed containers or moisture-proof packs, and may require the use of separate packages containing water-adsorbent agents, such as silica gel.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

For effervescent tablets, the label should state "Not to be swallowed directly".

Capsules. These should be packaged and stored in a manner that protects them from microbial contamination. Capsules should be kept in well-closed containers. They should be protected from light, excessive moisture, or dryness, and should not be subjected to temperatures above 30 °C.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

Parenteral preparations. These are usually supplied in glass ampoules, bottles or vials, plastic bottles or bags, and prefilled syringes, which are coloured in the case of light-sensitive substances.

Except where otherwise indicated in the relevant individual monographs, the containers for parenteral preparations should be made from a material that is sufficiently transparent to permit the visual inspection of the contents. They should not adversely affect the quality of the preparation, allow diffusion of any kind into or across the container, or release foreign substances into the preparation.

Closures for containers for parenteral preparations should be equipped with a firm seal to prevent the entry of microorganisms and other contaminants while permitting the withdrawal of a part or the whole of the contents without removal of the closure. They should not be made of materials that react with the contents, nor should they allow foreign substances to diffuse into the preparation. The elastomers of which the closure is made should be sufficiently firm to allow the passage of a needle with the least possible shedding of particles. Closures for multi-dose containers should be sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and thus protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened.

On visual inspection, solutions, reconstituted solutions and intravenous infusions (except dispersions) should be clear and free from visible particulate matter.

Topical semi-solid dosage forms. Containers for these dosage forms should be made from a material that does not adversely affect the quality of the preparation or allow diffusion of any kind into or across the container into the preparation. Closures for these containers should be of a design that minimizes microbial contamination and be equipped with a device that reveals whether the container has ever been opened.

Containers for topical semi-solid dosage forms should protect the preparation from light, moisture, and damage during handling and transportation. The use of suitable metal or plastic flexible tubes is preferred. Preparations for nasal, aural, vaginal or rectal use should be supplied in containers adapted for the appropriate delivery of the product to the site of application, or should be supplied with a suitable applicator.

Topical semi-solid dosage forms should be kept in well-closed containers. The preparation should maintain its pharmaceutical integrity throughout the shelf-life when stored at the temperature indicated on the label; this should normally not exceed 25 °C. Special storage recommendations or limitations are indicated in the relevant individual monographs.

5.2 *Pharmacopoeial requirements for containers in Europe, Japan and the USA*

5.2.1 *Glass containers*

As previously mentioned in section 2.1.1, a classification of types of glass for containers for pharmaceutical products does not exist in the Japanese pharmacopoeia, while those given in the European and United States pharmacopoeias are very similar.

Both the European and United States pharmacopoeias provide specifications for glass containers for injections. The latter publication also gives specific guidance for the packaging, repackaging and dispensing of medicinal products. Both the European and United States pharmacopoeias also provide specifications for light-resistant containers and tightly or well-closed closures for capsules and tablets.

The European pharmacopoeia gives a general account of the requirements for glass containers for pharmaceutical use, together with those specifically applicable to glass containers for human blood and blood products.

5.2.2 *Plastic containers*

Many different plastics are used for containers for medicinal products and the requirements applicable to them differ greatly in the various pharmacopoeias. It is very difficult to compare the tests described. Other and possibly different requirements may be found in international standards.

5.2.3 *Rubber closures*

A comparison of the requirements for rubber closures is as difficult as that for plastic containers. The European and Japanese pharmacopoeias contain special requirements for rubber closures intended for containers of aqueous parenteral preparations. The United States pharmacopoeia describes more generally the use of closures made from elastomers for injection bottles, but does not specify the preparations for which they can be used.

Similarities exist between the tests given in the European, Japanese and United States pharmacopoeias, but international standards also exist which differ considerably from one another.

5.3 *International Standards*

A list of recent International Standards on packaging is given in Appendix 4.

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Appendix 1
Storage areas[1]

1. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

2. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3. Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

4. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

5. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

6. Segregation should be provided for the storage of rejected, recalled or returned materials or products.

7. Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

8. Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling, and special attention should be paid to the safe and secure storage of these materials.

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[1] Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Appendix 2
Labels[1]

1. All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;

(b) a list of the active ingredients (if applicable, with the International Nonproprietary Names), showing the amount of each present, and a statement of the net contents, e.g. number of dosage units, weight or volume;

(c) the batch number assigned by the manufacturer;

(d) the expiry date in an uncoded form;

(e) any special storage conditions or handling precautions that may be necessary;

(f) directions for use, and warnings and precautions that may be necessary; and

(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

[1] Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Appendix 3
Self-inspection and quality audits[1]

1. *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively; all recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

2. Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) personnel
(b) premises including personnel facilities
(c) maintenance of buildings and equipment
(d) storage of starting materials and finished products
(e) equipment
(f) production and in-process controls
(g) quality control
(h) documentation
(i) sanitation and hygiene
(j) validation and revalidation programmes
(k) calibration of instruments or measurements systems
(l) recall procedures
(m) complaints management
(n) labels control
(o) results of previous self-inspections and any corrective steps taken.

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[1] Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Self-inspection team

3. Management should appoint a self-inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

4. The frequency at which self-inspections are conducted may depend on company requirements.

Self-inspection report

5. A report should be made at the completion of a self-inspection. The report should include:

(a) self-inspection results
(b) evaluation and conclusions
(c) recommended corrective actions.

Follow-up action

6. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

7. It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

Suppliers' audits

8. The quality control department should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

9. Before suppliers are approved and included in the specifications they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If the audit is required, it should determine the supplier's ability to conform with GMP standards for active pharmaceutical ingredients.

Appendix 4
International standards on packaging

A list is given below of the standards on packaging issued by the International Organization for Standardization (ISO), as of 10 October 1998, starting with the four main standards, after which they are listed in numerical order.

Quality systems — model for quality assurance in design, development, production, installation and servicing. International Standard ISO 9001. 1994.

Quality systems — model for quality assurance in production, installation and servicing. International Standard ISO 9002. 1994.

Quality systems — model for quality assurance in final inspection and test. International Standard ISO 9003. 1994.

Quality management and quality systems elements. Part 1: *Guidelines. International Standard ISO 9004-1*. 1994.

Quality management and quality systems elements. Part 2: *Guidelines for service. International Standard ISO 9004-2*. 1994.

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Quality management and quality systems elements. Part 4: *Guidelines for quality improvement. International Standard ISO 9004-4*. 1994.

Reusable all-glass or metal-and-glass syringes for medical use. Part 1: Dimensions. International Standard ISO 595-1. 1986.

Reusable all-glass or metal-and-glass syringes for medical use. Part 2: Design, performance requirements and tests. International Standard ISO 595-2. 1987.

Transfusion equipment for medical use. Part 1: Glass transfusion bottles, closures and caps. International Standard ISO 1135-1. 1987.

Plastics collapsible containers for human blood and blood components. International Standard ISO 3826. 1993.

Injection containers for injectables and accessories. Part 1: Injection vials made of glass tubing. International Standard ISO 8362-1. 1989.

Injection containers for injectables and accessories. Part 2: Closures for injection vials. International Standard ISO 8362-2. 1988.

Injection containers for injectables and accessories. Part 3: Aluminium caps for injection vials. International Standard ISO 8362-3. 1989.

Injection containers for injectables and accessories. Part 4: Injection vials made of moulded glass. International Standard ISO 8362-4. 1989.

Injection containers for injectables and accessories. Part 5: Freeze–drying closures for injection vials. International Standard ISO 8362-5. 1995.

Injection containers for injectables and accessories. Part 6: Caps made of aluminium–plastics combinations for injection vials. International Standard ISO 8362-6. 1992.

Injection containers for injectables and accessories. Part 7: Injection caps made of aluminium–plastics combinations without overlapping plastics part. International Standard ISO 8362-7. 1995.

Infusion equipment for medical use. Part 4: Infusion sets for single use, gravity feed. International Standard ISO 8536-4. 1998.

Infusion equipment for medical use. Part 5: Burette-type infusion sets. International Standard ISO 8536-5. 1992.

Infusion equipment for medical use. Part 6: Freeze–drying closures for infusion bottles. International Standard ISO 8536-6. 1995.

Infusion equipment for medical use. Part 7: Caps made of aluminium–plastics combinations for infusion bottles. International Standard ISO 8536-7. 1992.

Sterile single-use syringes, with or without needle, for insulin. International Standard ISO 8537. 1991.

Elastomeric parts for aqueous parenteral preparations. International Standard ISO 8871. 1990.

Aluminium caps for transfusion, infusion and injection bottles — general requirements and test methods. International Standard ISO 8872. 1988.

Injection equipment for medical use. Part 1: Ampoules for injectables. International Standard ISO 9187-1. 2000.

Injection equipment for medical use. Part 2: One-point-cut (OPC) ampoules. International Standard ISO 9187-2. 1993.

Dental cartridge syringes. International Standard ISO 9997. 1999.

Caps made of aluminium–plastics combinations for infusion bottles and injection vials — requirements and test methods. International Standard ISO 10985. 1999.

Prefilled syringes. Part 1: Glass cylinders for dental local anaesthetic cartridges. International Standard ISO 11040-1. 1992.

Prefilled syringes. Part 2: Plungers and discs for dental local anaesthetic cartridges. International Standard ISO 11040-2. 1994.

Prefilled syringes. Part 3: Aluminium caps for dental local anaesthetic cartridges. International Standard ISO 11040-3. 1993.

Prefilled syringes. Part 4: Glass barrels for injectables. International Standard ISO 11040-4. 1996.

Prefilled syringes. Part 5: Plungers for injectables. International Standard ISO 11040-5. 1996.

Containers and accessories for pharmaceutical preparations. Part 1: Drop-dispensing bottles. International Standard ISO 11418-1. 1996.

Containers and accessories for pharmaceutical preparations. Part 2: Screw-neck bottles for syrups. International Standard ISO 11418-2. 1996.

Containers and accessories for pharmaceutical preparations. Part 3: Screw-neck bottles (vials) for solid and liquid dosage forms. International Standard ISO 11418-3. 1996.

Containers and accessories for pharmaceutical preparations. Part 4: Tablet bottles. International Standard ISO 11418-4. 1996.

Containers and accessories for pharmaceutical preparations. Part 5: Dropper assemblies. International Standard ISO 11418-5. 1997.

Containers and accessories for pharmaceutical preparations. Part 7: Screw-neck vials made of glass tubing for liquid dosage forms. International Standard ISO 11418-7. 1998.

Pen-injectors for medical use. Part 1: Requirements and test methods. International Standard ISO 11608-1. 2000.

Pen-injectors for medical use. Part 2: Needles — requirements and test methods. International Standard ISO 11608-2. 2000.

Pen-injectors for medical use. Part 3: Finished cartridges — requirements and test methods. International Standard ISO 11608-3. 2000.

Pen systems. Part 1: Glass cylinders for pen-injectors for medical use. International Standard ISO 13926-1. 1998.

Pen systems. Part 2: Plungers and discs for pen-injectors for medical use. International Standard ISO 13926-2. 1999.

Disposable hanging devices for transfusion and infusion bottles — requirements and test methods. International Standard ISO 15010. 1998.

WHO Technical Report Series, No. 902, 2002

Annex 10
Model certificate of analysis

It has been recommended in various fora that WHO should establish a model certificate of analysis for use in trade in starting materials and by manufacturers of pharmaceutical substances, excipients and medicinal products. A model of such a certificate is shown in Appendix 1. The items included are based on good practices for national pharmaceutical control laboratories and good manufacturing practices (GMP) for pharmaceutical products (*1*). The certificate lists the results and includes a final evaluation and the conclusions of the examination of one or more samples.

In accordance with GMP, the certificate can be used in lieu of testing by the manufacturer (except for the identification tests as a minimum requirement), provided that the reliability of the supplier's analysis is established by the periodic validation of the test results by appropriate means and, if feasible, by on-site audits of the supplier's capabilities. Certificates must be originals (not copies or duplicates) or their authenticity must otherwise be assured, i.e. they must be issued by the supplier of the material concerned (manufacturer, broker, etc.), or based on the analytical worksheet of the laboratory testing the sample(s). For further details, see Annex 3.

The certificate should include:

- The name and address of the laboratory performing the tests.
- The registration number of the certificate of analysis.
- The name, description (i.e. grade, quantity received, type of container) and number (used by the original manufacturer and repacker/trader) of the batch for which the certificate is issued, the date of manufacture, and the expiry date (or retest date).
- The date on which the batch for which the certificate is issued was received.
- A reference to the test procedure used, including the acceptance criteria (limits).
- The results of all tests performed on the batch for which the certificate is issued (in numerical form, where applicable) and a comparison with the established acceptance criteria (limits).

- Any additional test results obtained on samples from the batch as part of a periodic statistically based testing programme.
- A statement indicating whether the results were found to comply with the requirements.
- The date(s) on which the test(s) was (were) performed.
- The signature of the head of the laboratory or an authorized person.
- The name, address, and telephone and fax numbers of the original manufacturer. If supplied by repackers or traders, the certificate should show the name, address, and telephone and fax numbers of the repacker/trader and a reference to the original manufacturer.
- A statement of the expected conditions of shipping, packaging, storage and distribution, deviation from which would invalidate the certificate.
- A copy of the certificate generated by the original manufacturer, if the sample is supplied by a repacker or trader.

Reference

1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Appendix 1

Model certificate of analysis for active pharmaceutical ingredients, excipients and medicinal products

Registration number of sample or certificate: _____

Name and address of laboratory testing the sample:

_____

_____

_____

Sample information

Name of product (INN, brand name(s), etc.):

_____

Dosage form (if applicable): _____

_____

Marketing authorization number (if applicable): _____

Description (appearance of container and contents):

_____

_____

_____

_____

Batch number(s): _____

Required storage conditions:[1] _____

Date received: _____ Date of manufacture: _____

Expiry date (for medicinal products) or retest date (for starting materials or excipients): _____

Name and address of original manufacturer:

_____

_____

Telephone: _____ Fax: _____

Name and address of repacker and/or trader (if applicable):

Telephone: Fax:

Test procedure (reference to test procedure) (if applicable)	Result (numerical result)[2] (if applicable)	Acceptance criteria (limits)
A. Tests performed on samples from batch for which certificate is issued		
B. Tests performed as part of periodic statistically based testing programme		

Conclusions:

Compliance with acceptance criteria: yes☐ no☐

Date test performed/finalized:

Name and address of head of laboratory/authorized person:

Telephone: Fax:

Signature:

Explanatory notes

[1] Statement of expected conditions of shipping, packaging, storage and distribution, deviation from which could render the certificate invalid.

[2] Indicate if the results were obtained from periodic statistically based testing.

WHO Technical Report Series, No. 902, 2002

Annex 11
Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products

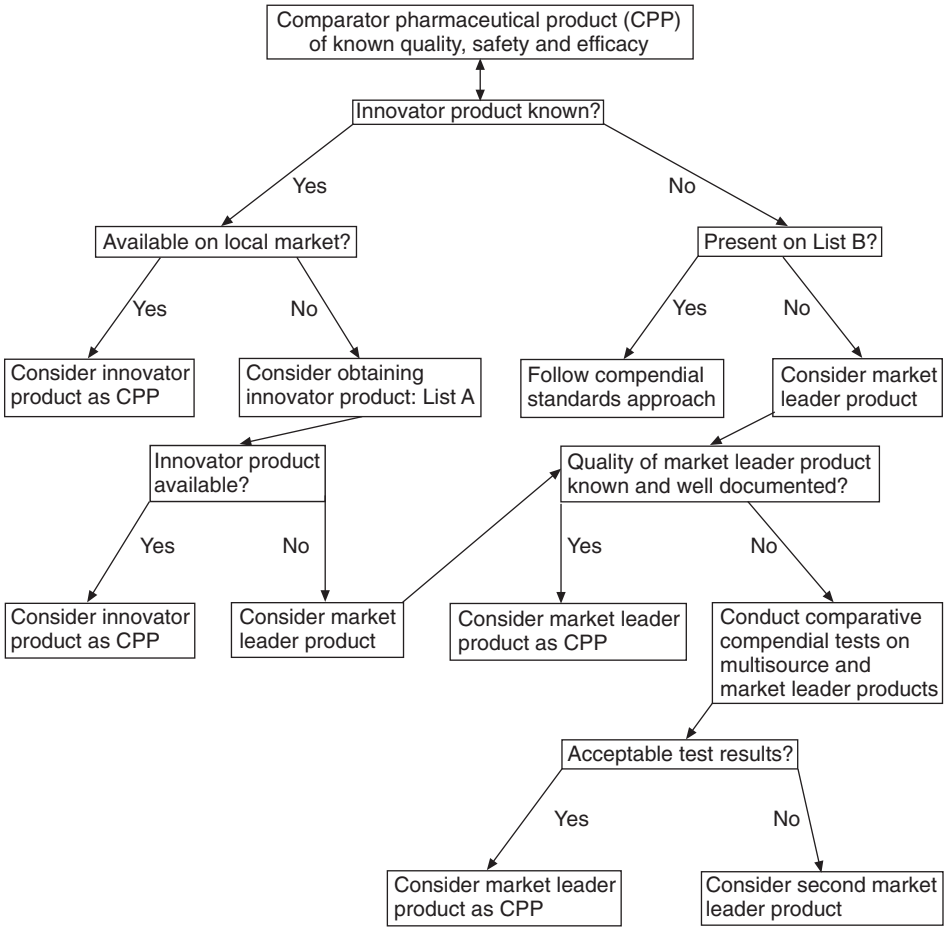
Introduction

This annex provides a list of comparator products for equivalence assessment of interchangeable multisource (generic) products. The information on comparator pharmaceutical products was collected by the Secretariat from drug regulatory authorities and pharmaceutical companies. The list has been drawn up to assist regulatory authorities and pharmaceutical companies in deciding on appropriate comparator products in the context of multisource (generic) marketing authorization. The information could also be used for drug procurement purposes. Where the comparator pharmaceutical product is not clearly defined, criteria are suggested that are provided in a decision-tree format (see Figure 1). This permits the selection of a comparator pharmaceutical product.

The guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products published by WHO (*1*) state that multisource products must satisfy the same standards of quality, safety and efficacy as those applicable to the corresponding innovator product. They recommend that quality attributes of a multisource product should be tested against the innovator product for which interchange is intended.

The innovator product is usually the most logical comparator product because its quality, safety and efficacy should have been well assessed in pre- and post-marketing studies and, in addition, the data on its safety and efficacy are usually linked to a pharmaceutical product with defined specifications for quality and performance. Despite acceptance of the general objective, there is no agreement on the criteria for selecting a list of international comparator products, nor does a list of such products exist. The comparator product chosen is either the most widely used "leading" product on the market or the product that was first introduced in that market. For this reason, among others, significant differences may exist between the comparator products used in different countries.

Figure 1
Decision-tree for use in identifying a comparator pharmaceutical product



In the light of the various approaches currently under scientific and regulatory discussion, the feasibility of developing a system of international comparator products was considered. This initiative led to the recommendations given here, which replace those of Part Seven of the previously published WHO guidelines on multisource pharmaceutical products (*1*).

A list of international comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products[1] is given in Table 1.

[1] The list is based on information collected by WHO from drug regulatory authorities and supplemented with that from pharmaceutical companies. It will be periodically updated.

Instructions on the use of the list

1. National regulatory authorities may issue this guidance together with Lists A and B, which should be available to applicants/pharmaceutical companies that plan to develop multisource pharmaceutical products intended to be interchangeable with innovator or other pharmaceutical products of established quality, safety and efficacy.

2. List A provides information about pharmaceutical products from the WHO Model List of Essential Drugs (*2*), and includes the innovator products (column headed "Trademark") and the national markets where the manufacturers in question consider that their products' quality, safety and efficacy are best documented (column headed "Primary market").

3. Pharmaceutical companies planning to develop an interchangeable multisource pharmaceutical product should determine whether the innovator pharmaceutical product appearing in List A is available on the local market.

4. If the innovator pharmaceutical product is available on the local market, pharmaceutical companies should use this product in equivalence assessment with their multisource product.

5. If the innovator product is not available on the local market, pharmaceutical companies should obtain from the market a product that is the best representative innovator product from the point of view of its quality, safety and efficacy (see column headed "Primary market" of List A).

6. The type of equivalence assessment of the comparator pharmaceutical product and the multisource product under investigation may vary, depending on local requirements and the availability of resources. Recommendations on the type of equivalence studies to be carried out when such studies are necessary are given in the WHO guidelines on multisource pharmaceutical products (*1*).

7. For some pharmaceutical products, an innovator product cannot be identified. Examples of these products from the WHO Model List of Essential Drugs (*2*) appear in List B. For these products, a local, national or regional pharmacopoeia or *The international pharmacopoeia* (*3*) for both the drug substance and, when available, the product, supplemented by official reference texts, may provide sufficient information and requirements to allow a pharmaceutical company to develop a product of the requisite quality, safety and efficacy. No international comparator product for these

pharmaceutical products will be available, and no equivalence assessment can be performed.

Also included in List B are pharmaceutical products for which an innovator product can be identified or a marker leader product may be available, but for which there is insufficient information available for them to appear in List A, e.g. products for which the originator no larger exists or which cannot be traced. The List A approach can also be applied to these products.

8. When a market leader product is available on the local market but no innovator product can be identified or obtained from the primary market, the market leader product may be used as a comparator product if its quality, safety and efficacy have been established. If this is not the case, the second market leader or compendial standards approach (List B) can be followed.

Most of the pharmaceuticals listed are included in the WHO Model List of Essential Drugs (*2*). In the case of products for which equivalence testing is required, it should be performed in accordance with the WHO guidelines on registration requirements to establish interchangeability of multisource (generic) products (*1*).

Layout of the list

Pharmaceutical name (1)	Section no. (2)	Dosage forms and strengths (3)	Comparator pharmaceutical products (4)		
			Trademark	Primary market	Manufacturer
albendazole	6.1.1	chtab, 200 mg	Zentel	France	SmithKline Beecham

The list is divided into two parts, as follows:

- *List A* provides information on comparator pharmaceutical products — trademark and primary market — as given by manufacturers of innovator products.
- *List B* contains products for which information has not been given by manufacturers of innovator or market leader products or difficulties in providing the information were encountered because the pharmaceutical products have been marketed for a long time.

(1) Pharmaceutical name: International Nonproprietary Names (INNs) are used to identify the active drug substance as in the WHO Model List of Essential Drugs.

(2) Section no.: this corresponds to the WHO Model List of Essential Drugs, and indicates the therapeutic uses/pharmacological effects of the pharmaceutical.

(3) Dosage forms and strengths: these correspond to the WHO Model List of Essential Drugs. A strike-through means that no products of the dosage form or strength are available on the market. An entry in bold signifies that a product of the dosage form or strength is available on the market instead of, or in addition to, those in the WHO Model List of Essential Drugs.

The following abbreviations are used:

cap	capsule
chcap	chewable capsule
chtab	chewable tablet
cre	cream
elix	elixir
encotab	enteric-coated tablet
eyd	eye drop
eyo	eye ointment
inh	inhalation
inj	injection/injectable solution
lot	lotion
loz	lozenge
multi	multiple
nsp	nasal spray
oilinj	injection in oil
oilsl	oily solution
oilsp	oil suspension
oilspinj	oil suspension injection
oin	ointment
oosl	oral oily solution
osl	oral solution
osp	oral suspension
pes	pessary
pwinj	powder for injection
pwosp	powder for oral suspension
pwsl	powder for solution
respsl	respirator solution
sbltab	tablet, sublingual
sctab	scored tablet
sgtab	sugar-coated tablet
sl	solution
sr	sustained-release preparation

sup	suppository
syr	syrup
tab	tablet
topsl	solution, topical
vagtab	vaginal tablet
wminj	water-miscible injection

(4) Comparator pharmaceutical products: "Trademark" and "Primary market" for List A indicate the innovator products and the national markets where the manufacturers in question consider that their products' quality, safety and efficacy are best documented.

List B, which does not give this information, follows the pharmacopoeial standards approach.

The entry ***** means that additional information on the product must be provided before it can be included in List A.

Table 1
International comparator products for equivalence assessment of interchangeable multisource (generic) products[a]

Pharmaceutical name	Section no.	Dosage forms and strengths	Comparator pharmaceutical products		
			Trademark	Primary market	Manufacturer
List A					
albendazole	6.1.1	chtab, 200mg	Zentel	France	SmithKline Beecham
amiloride, hydrochloride	16	tab, 5mg	Midamor	United Kingdom	Merck, Sharp & Dohme
aminophylline	25.1	tab, 100mg, 200mg (sr), 125mg	Aminophylin	Germany	BYK Gulden Lomberg
amitriptyline, hydrochloride	24.2.1	tab, 25mg	Elavil	USA	Zeneca
amoxicillin	6.2.1	cap, 250mg, 500mg pwosp, 125mg/5ml tab, 250mg, 500mg	Amoxil	United Kingdom	SmithKline Beecham
atenolol	12.1 12.2 12.3	tab, 50mg, 100mg tab, 50mg, 100mg tab, 50mg, 100mg	Tenormin	United Kingdom	Zeneca
atropine, sulfate	21.5	eyd, ~~0.1%~~, 0.5%, 1%	Atropin Dispersa	Switzerland	Ciba Vision (Novartis)
benznidazole	6.5.5	tab, 100mg	Radanil	Argentina, Brazil, Switzerland	Roche
biperiden, hydrochloride	9	tab, 2mg	Akineton	Germany	Knoll
captopril	12.3	sctab, 25mg	Capoten	USA	Bristol-Myers Squibb
carbamazepine	5	sctab, 100mg, 200mg (sr)	Tegretol	Switzerland	Novartis
chloramphenicol	6.2.2	cap, 250mg	Chloromycetin	USA	Parke-Davis
chloramphenicol, sodium succinate	6.2.2	oilspinj, 0.5g/2ml	Chloromycetin sodium succinate	USA	Parke-Davis/Parkedale
chloroquine, phosphate	6.5.3	tab, 25mg, 100mg,[b] 150mg,[b,c] 500mg	Alaren phosphate	USA	Sanofi Winthrop
chlorphenamine, hydrogen maleate	3	tab, 4mg	Chlortrimeton	USA	Schering-Plough
ciclosporin	8.1	cap, 25mg	Sandimmun	Switzerland	Novartis

Table 1 (*continued*)

Pharmaceutical name	Section no.	Dosage forms and strengths	Comparator pharmaceutical products		
			Trademark	Primary market	Manufacturer
cimetidine	17.1	tab, 200mg	Tagamet	France	SmithKline Beecham
ciprofloxacin, hydrochloride	6.2.2	tab, 250mg	Ciprobay	Germany	Bayer
clofazimine	6.2.3	cap, 50mg, 100mg	Lamprene	Switzerland	Novartis
clomifene, citrate	18.6	tab, 50mg	Clomid	USA	Hoechst Marion Roussel
clomipramine, hydrochloride	24.4	cap, 10mg, 25mg	Anafranil	Switzerland	Novartis
clonazepam	5	sctab, 500µg	Rivotril	Switzerland	Roche
cloxacillin, sodium	6.2.1	cap, 500mg pwsl, 125mg/5ml	Penstaphon Tegopen	Belgium USA	Bristol-Myers Squibb
cyclophosphamide	8.2	tab, 25mg, 50mg	Endoxana	United Kingdom	ASTA Medica
dapsone	6.2.3	tab, **25 mg**, ~~50 mg~~, 100mg	Dapsone	USA	Jacobus
desmopressin, acetate	10.2	nsp, 10µg/metered dose	DDAVP	USA	Ferring
dexamethasone	3 18.1	tab, 500µg, 4mg tab, 500µg, 4mg	Decadron	USA	Merck, Sharp & Dohme
diazepam	24.3	sctab, 2mg, 5mg	Valium	USA	Roche
doxazosin mesilate	12.3	tab, 1mg, 2mg, 4mg	Caldura	Germany	Pfizer
doxycycline, hyclate	6.2.2	cap, 100mg tab, 100mg	Vibramycin	Germany	Pfizer
epinephrine, hydrochloride	21.5	eyd, 2%	Suprarenin	Germany	Hoechst Marion Roussel
ergocalciferol	27	cap, 1.25mg (50000IU) osl, 250µg/ml (10000IU/ml) tab, 1.25mg (50000IU)	Drisdol	USA	Sanofi
ethinylestradiol	18.4	tab, 10µg, 20µg, 50µg	Pregynon C	Germany	Schering
ethinylestradiol + levonorgestrel	18.3.1	tab, 30µg + 150µg, 50µg + 250µg	Nordette-21	USA	Wyeth-Ayerst

ethosuximide	5	cap, 250mg syr, 250mg/5ml	Zarontin	USA	Parke-Davis
etoposide	8.2	cap, 100mg inj, 20mg/ml, ~~50mg/ml~~	Vepesid	Netherlands USA	Bristol-Myers Squibb
flucytosine	6.3	cap, 250mg	Ancobon	USA	ICN Pharmaceuticals
fludrocortisone, acetate	18.1	tab, 100µg	Florinef	USA	Bristol-Myers Squibb
fluorouracil	13.5	oin, 5%	Efudix	USA	Roche
fluphenazine, decanoate	24.1	depot inj, 25mg/ml	Prolixin decanoate	USA	Bristol-Myers Squibb
fluphenazine, enantate	24.1	depot inj, 25mg/ml	Prolixin enanthate	USA	Bristol-Myers Squibb
furosemide	16	tab, 40mg	Lasix	Germany	Hoechst Marion Roussel
glyceryl trinitrate	12.1	~~sbltab~~, ~~500µg~~ **chcap, 800µg**	Nitroglycerin Wander	Switzerland	Novartis
griseofulvin	6.3	cap, 125mg, 250mg tab, 125mg, 250mg	Grisactin Fulcin	USA USA	Zeneca
haloperidol	24.1	tab, 2mg, 5mg	Haldol	Belgium	Janssen
hydralazine, hydrochloride	12.3	tab, 25mg, 50mg pwinj, 20mg	Apresoline	Netherlands United Kingdom	Novartis
hydrochlorothiazide	12.3 16	tab, 25mg tab, 25mg, 50mg	Hydrosaluric	United Kingdom	Merck, Sharp & Dohme
ibuprofen	2.1	tab, 200mg	Nurofen	UK	Boots
idoxuridine	21.1	eyd, 0.1% eyo, 0.2%	Herplex	USA	Allergan
imipenem (monohydrate) + cilastin (sodium)	6.2.1	pwinj, 250mg + 250mg, 500mg + 500mg pwinj, 500mg + 500mg	Tienam	Italy	Merck, Sharp & Dohme
insulin injection (soluble)	18.5	inj, 40IU/ml, ~~80IU/ml, 100IU/ml~~	Actrapid	Germany	Novo Nordisk
		inj, ~~40IU/ml~~, ~~80IU/ml,~~ 100IU/ml	Actrapid	Zimbabwe	
		inj, ~~40IU/ml~~, ~~80IU/ml,~~ 100IU/ml	Novolin R	Japan, USA	

Table 1 (*continued*)

Pharmaceutical name	Section no.	Dosage forms and strengths	Comparator pharmaceutical products		
			Trademark	Primary market	Manufacturer
intermediate-acting insulin (as compound insulin zinc suspension)	18.5	inj, 40 IU/ml, 80 IU/ml, 100 IU/ml	Humulin L	USA	Eli Lilly
intermediate-acting insulin (as isophane insulin)	18.5	inj, 40 IU/ml, 80 IU/ml, 100 IU/ml	Humulin N	USA	Eli Lilly
ipratropium bromide	25.1	inh, 20 µg/metered dose	Atrovent	USA	Boehringer Ingelheim
iron dextran	10.1	inj, equiv. to 50 mg iron/ml	Infed	USA	Shein Pharmaceuticals
isosorbide dinitrate	12.1	sbltab, 5 mg	Isordil	USA	Wyeth-Ayerst
ivermectin	6.1.2	sctab, 6 mg	Mectizan/Stromectol	Netherlands	Merck, Sharp & Dohme
ketoconazole	6.3	osp, 100 mg/5 ml tab, 200 mg	Nizoral	Belgium	Janssen
levamisole, hydrochloride	6.1.1 8.2	tab, 50 mg, 150 mg tab, 50 mg	Ergamisol	Belgium	Janssen
levodopa + carbidopa	9	tab, 100 mg + 10 mg, 250 mg + 50 mg	Sinemet	Italy	Merck, Sharp & Dohme
levonorgestrel	18.3.1	tab, 30 µg	Microval	Germany	Wyeth-Ayerst
lithium carbonate	24.2.2	cap, 300 mg tab, 300 mg	Quilonum	Germany	SmithKline Beecham
mebendazole	6.1.1	chtab, 100 mg, 500 mg	Vermox	Belgium	Janssen
medroxyprogesterone acetate	18.3.1 18.7	depot inj, 150 mg/ml tab, 5 mg	Depo-Provera Provera	USA	Pharmacia-Upjohn
mefloquine, hydrochloride	6.5.3	tab, 250 mg	Lariam	Switzerland	Roche
methyldopa	12.3	tab, 250 mg	Aldomet	Spain	Merck, Sharp & Dohme
metoclopramide, hydrochloride	17.2	tab, 10 mg	Primperan	France	Synthlabo

miconazole, nitrate	13.1	cre, 2% oin, 2%	Daktarin	Belgium	Janssen
nalidixic acid	6.2.2	~~tab~~, ~~500 mg~~ **cap, 500 mg**	Neggran	USA	Sanofi Winthrop
neostigmine, bromide	20	tab, 15 mg	Prostigmin	Germany	Roche
niclosamide	6.1.1	chtab, 500 mg	Yomesan	Germany	Bayer
nifedipine	12.3	cap, 10 mg (sr) tab, 10 mg (sr)	Adalat 10 Adalat T 10	Germany	Bayer
nifurtimox	6.5.5	tab, 30 mg, 120 mg, ~~250 mg~~	Lampit	Argentina	Bayer
nitrofurantoin	6.2.2	tab, 100 mg	Furadantin	Ireland, United Kingdom	Proctor & Gamble
norethisterone enantate	18.3.1	oilsl, 200 mg/ml	Noristerat	Mexico, South Africa	Schering
nystatin	6.3	loz, 100 000 IU ~~pes~~, ~~100 000 IU~~ tab, 100 000 IU tab, 500 000 IU **vagtab, 100 000 IU**	Nystan Mycostatine	United Kingdom France France USA France	Bristol-Myers Squibb
oxamniquine	6.1.3	cap, 250 mg syr, 250 mg/5 ml	Mansil/Vansil	Brazil	Pfizer
paracetamol	2.1	sup, ~~100 mg~~, **125 mg, 250 mg, 500 mg, 1000 mg**	Ben-U-Ron	Germany	Bene
penicillamine	4.2	cap, 250 mg tab, 250 mg	Cuprimine Depen	USA	Merck, Sharp & Dohme Cater-Wallace
phenobarbital	5	tab, 15–100 mg	Luminal (100 mg) Luminaletten (15 mg)	Germany	Desitin
phenoxymethylpenicillin, potassium	6.2.1	pwosp, 250 mg/5 ml tab, 250 mg	V-Cillin K	USA	Eli Lilly
phenytoin, sodium	5	cap, ~~25 mg,~~ **30 mg**, ~~50 mg,~~ 100 mg tab, ~~25 mg,~~ 50 mg, ~~100 mg~~	Dilantin Kapseals Dilantin Infatabs	USA	Parke-Davis
phytomenadione	10.2	tab, 10 mg	Konakion	Switzerland	Roche

Table 1 (*continued*)

Pharmaceutical name	Section no.	Dosage forms and strengths	Comparator pharmaceutical products		
			Trademark	Primary market	Manufacturer
praziquantel	6.1.1	tab, 150 mg, 600 mg	Biltricide	Germany	Bayer
	6.1.3	tab, 600 mg			
prednisolone	3	tab, 5 mg	Scherisolon	Colombia, Uruguay	Schering
	8.3	tab, 5 mg			
	18.1	tab, 1 mg, 5 mg			
	21.2	eyd, 0.5%	Ultracortenol	Germany	Ciba Vision (Novartis)
procainamide, hydrochloride	12.2	tab, 250 mg, 500 mg	Pronestyl	USA	Bristol-Myers Squibb
procarbazine, hydrochloride	8.2	cap, 50 mg	Natulan	Switzerland	Roche
proguanil, hydrochloride	6.5.3	tab, 100 mg	Paludrine	United Kingdom	Zeneca
propranolol, hydrochloride	7.2	tab, 20 mg, 40 mg	Inderal	Japan	Zeneca
	—	tab, 10 mg, 40 mg		United Kingdom	
pyrantel, embonate	6.1.1	chtab, 250 mg osp, 50 mg/ml	Combantrin	Germany	Pfizer
pyrazinamide	6.2.4	tab, ~~400 mg.~~ **500 mg**	Zinamide	United Kingdom	Merck, Sharp & Dohme
pyridostigmine, bromide	20	tab, 60 mg	Mestinon	Switzerland	Roche
rifampicin	6.2.3	cap, 150 mg, 300 mg tab, 150 mg, 300 mg	Rifadin	Italy	Gruppo Lepetit
	6.2.4	cap, 150 mg, 300 mg tab, 150 mg, 300 mg			
rifampicin + isoniazid	6.2.4	tab, 150 mg + 100 mg, 300 mg + 150 mg	Rifinah	Italy	Gruppo Lepetit
rifampicin + isoniazid + pyrazinamide	6.2.4	tab, 150 mg + 75 mg + 400 mg, 150 mg + 150 mg + 500 mg	Rifater	Italy	Hoechst Marion Roussel
silver sulfadiazine	13.2	cre, 1%/500 g	Silvadene	USA	Hoechst Marion Roussel

sulfadoxine + pyrimethamine	6.5.3	tab, 500 mg + 25 mg	Fansidar	Switzerland	Roche
sulfamethoxazole + trimethoprim	6.2.2	osp, 200 mg + 40 mg/5 ml tab, 100 mg + 20 mg, 400 mg + 80 mg	Bactrim	Switzerland	Roche
sulfasalazine	17.4	tab, 500 mg	Azulfidine	USA	Pharmacia-Upjohn
tamoxifen, citrate	8.3	tab, 10 mg, 20 mg	Nolvadex	United Kingdom	Zeneca
testosterone, enantate	18.2	inj, 200 mg/ml, **250 mg/ml**	Testorion depot	Argentina, Germany, Mexico	Schering
theophylline	25.1	tab, ~~100 mg~~, **125 mg**, ~~200 mg~~, **250 mg, 375 mg, 500 mg**	Euphylong	Germany	BYK-Gulden
timolol, maleate	21.4	**sl** (eyd), 0.25%, 0.5%	Timoptol ophthalmic solution	France	Merck, Sharp & Dohme
		eyd, 0.25%, 0.5% **(unit dose)**	Timoptol Ocudose		
		gel (eyd), 0.25%, 0.5%	Timoptol LP		
tolbutamide	—	tab, 500 mg	Rastinon	Germany	Hoechst Marion Roussel
triclabendazole	6.1.3	tab, 250 mg	Egaten	Egypt	Novartis
tropicamide	14.1	eyd, 0.5%	Mydriacyl	United Kingdom	Alcon
verapamil, hydrochloride	12.1	tab, 40 mg, 80 mg (sr)	Isoptin	Germany	Knoll
	12.2	tab, 40 mg, 80 mg (sr)			

List B

acetazolamide	21.4	tab, 250 mg	*****
acetylsalicylic acid	2.1	sup, 50–150 mg	*****
		tab, 100–500 mg	*****
	7.1	tab, 300–500 mg	*****
	12.5	tab, 100 mg	*****
aciclovir	6.4.1	tab, 200 mg	*****
aciclovir (sodium)	6.4.1	pwinj, 250 mg	*****
allopurinol	2.3	tab, 100 mg	*****
aluminium hydroxide	17.1	osp, 320 mg/5 ml tab, 500 mg	

Table 1 (*continued*)

Pharmaceutical name	Section no.	Dosage forms and strengths	Comparator pharmaceutical products		
			Trademark	Primary market	Manufacturer
amoxicillin + clavulanic acid	6.2.1	tab, 500mg + 125mg	*****		
ascorbic acid	27	tab, 50mg			
atropine, sulfate	17.5	tab, 1mg	*****		
azathioprine	8.1	tab, 50mg	*****		
beclometasone, dipropionate	25.1	inh, 50μg/dose	*****		
benzoic acid + salicylic acid	13.1	cre, 6% + 3% oin, 6% + 3%			
benzoyl peroxide	13.5	cre, 5% lot, 5%			
benzoyl benzoate	13.6	lot, 25%			
betamethasone, valerate	13.3	cre, 0.1%	*****		
		oin, 0.1%	*****		
calamine lotion	13.3	lot			
chloral hydrate	1.3	syr, 200mg/5ml			
chloramphenicol, palmitate	6.2.2	osp, 150mg/5ml	*****		
chloroquine, phosphate	6.5.3	syr, 50mg/5ml[b,c]	*****		
chloroquine, sulfate	6.5.3	syr, 50mg/5ml[b,c] tab, 100mg,[b] 150mg[b,c]			
chlorpromazine, hydrochloride	24.1	syr, 25mg/5ml	*****		
		tab, 100mg	*****		
coal tar	13.5	topsl, 5%			
codeine, phosphate	2.2	tab, 30mg	*****		
	17.7.2	tab, 30mg	*****		
colchicine	2.3	tab, 500μg	*****		

cromoglicic acid, sodium	25.1	inh, 20mg/dose	*****
dextromethorphan	25.2	osl, 3.5mg/5ml	*****
diethylcarbamazine, dihydrogen citrate	6.1.2	tab, 50mg	*****
diethyltoluamide	6.6	topsl, 50%, 75%	
digitoxin	—	tab, 50µg, 100µg	*****
digoxin	12.4	osl, 50µg/ml	*****
		tab, 62.5µg, 250µg	*****
diloxanide, furoate	6.5.1	tab, 500mg	*****
dimercaprol	4.2	oilinj, 50mg/ml	*****
dithranol	13.5	oin, 0.1–2%	*****
ergometrine, hydrogen maleate	22.1	tab, 200µg	*****
ergotamine, tartrate	7.1	tab, 1mg	
erythromycin, ethyl succinate	6.2.2	cap, 250mg	*****
		pwosp, 125mg	*****
		tab, 250mg	*****
erythromycin, stearate	6.2.2	cap, 250mg	*****
		pwosp, 125mg	*****
		tab, 250mg	*****
ethambutol, hydrochloride	6.2.4	tab, 100–400mg	*****
ethinylestradiol + norethisterone	18.3.1	tab, 35µg + 1.0mg	*****
ferrous salt, sulfate	10.1	osl, equiv. to 25mg iron/ml	
		tab, equiv. to 60mg iron	
ferrous salt (sulfate) + folic acid	10.1	tab, equiv. to 60mg iron + 250µg folic acid	
folic acid	10.1	tab, 1mg, 5mg	*****
gentamicin, sulfate	21.1	eyd, 0.3%	*****
glibenclamide	18.5	tab, 2.5mg, 5mg	*****

Table 1 (*continued*)

Pharmaceutical name	Section no.	Dosage forms and strengths	Comparator pharmaceutical products		
			Trademark	Primary market	Manufacturer
hydrocortisone, acetate	13.3	cre, 1%	*****		
		oin, 1%	*****		
	17.4	supp, 25mg	*****		
hydrogen peroxide	—	sl, 3%			
iopanoic acid	14.2	tab, 500mg	*****		
ipecacuanha	4.1	syr, 0.14%, as emetine			
isoniazid	6.2.4	tab, 100–300mg	*****		
isoniazid + ethambutol	6.2.4	tab, 150mg + 400mg	*****		
levothyroxine, sodium	18.8	tab, 50µg, 100µg	*****		
magnesium hydroxide	17.1	osp, equiv. to 550mg/10ml			
mercaptopurine	8.2	tab, 50mg	*****		
metformin	18.5	tab, 500mg	*****		
DL-methionine	4.2	tab, 250mg	*****		
methotrexate, sodium	8.2	tab, 2.5mg	*****		
metrifonate	—	tab, 100mg	*****		
metronidazole	6.2.2	sup, 500mg, 1g	*****		
		tab, 200–500mg	*****		
	6.5.1	tab, 200–500mg	*****		
metronidazole, benzoate	6.5.1	osp, 200mg/5ml	*****		
morphine, hydrochloride	2.2	osl, 10mg/5ml			
morphine, sulfate	2.2	osl, 10mg/5ml			
		tab, 10mg			
neomycin, sulfate + bacitracin zinc	13.2	oin, 5mg + 500IU	*****		
nicotinamide	27	tab, 50mg			
norethisterone	18.7	tab, 5mg	*****		
paracetamol	2.1	syr, 125mg/5ml			
		tab, 100–500mg			
	7.1	tab, 300–500mg			

permethrin	13.6	lot, 1%	
pethidine, hydrochloride	2.2	tab, 50mg, 100mg	*****
phenobarbital	5	elix, 15mg/5ml	*****
pilocarpine, hydrochloride or nitrate	21.4	sl (eyd), 2%, 4%	*****
podophyllum resin	13.5	topsl, 10–25%	
potassium iodide	18.8	tab, 60mg	
primaquine, diphosphate	6.5.3	tab, 7.5mg, 15mg	*****
promethazine, hydrochloride	1.3	elix, 5mg/5ml	*****
		syr, 5mg/5ml	*****
	17.2	elix, 5mg/5ml	*****
		syr, 5mg/5ml	*****
		tab, 10mg, 25mg	*****
propyliodone	14.2	oilsp, 500–600mg/ml	*****
propylthiouracil	18.8	tab, 50mg	*****
pyridoxine, hydrochloride	27	tab, 25mg	
quinidine, sulfate	12.2	tab, 200mg	*****
quinine, bisulfate	6.5.3	tab, 300mg	
quinine, sulfate	6.5.3	tab, 300mg	
reserpine	12.3	tab, 100µg, 250µg	*****
retinol, palmitate	27	cap, 200000IU (110mg)	
		oosl, 100000IU/ml	
		sgtab, 10000IU (5.5mg)	
		wminj, 100000IU/2ml (55mg)	
riboflavin	27	tab, 5mg	
salbutamol, sulfate	22.2	tab, 4mg	*****
	25.1	inh, 100µg/dose	*****
		respsl, 5mg/ml	*****
		syr, 2mg/5ml	*****
		tab, 2mg, 4mg	*****
salicylic acid	13.5	topsl, 5%	

Table 1 (*continued*)

Pharmaceutical name	Section no.	Dosage forms and strengths	Comparator pharmaceutical products		
			Trademark	Primary market	Manufacturer
senna (sennoside)	17.6	tab, 7.5 mg			
silver nitrate	21.1	sl (eyd), 1%			
sodium fluoride	27	any			
spironolactone	16	tab, 25 mg	*****		
sulfadiazine	6.2.2	tab, 500 mg	*****		
sulfadimidine	—	osp, 500 mg/5 ml	*****		
		tab, 500 mg	*****		
tetracaine, hydrochloride	21.3	sl (eyd), 0.5%	*****		
tetracycline, hydrochloride	21.1	eyo, 1%	*****		
thiamine, hydrochloride	27	tab, 50 mg			
thioacetazone + isoniazid	6.2.4	tab, 50 mg + 100 mg, 150 mg + 300 mg	*****		
trimethoprim	6.2.2	tab, 100 mg, 200 mg	*****		
urea	13.5	cre, 10%			
		oin, 10%			
valproic acid, sodium	5	encotab, 200 mg, 500 mg	*****		
warfarin, sodium	10.2	tab, 1 mg, 2 mg, 5 mg	*****		
zidovudine	6.4.2	cap, 100 mg, 250 mg	*****		
		osl, 50 mg/5 ml	*****		
zinc oxide	—	cre			
		oin			

[a] For instructions on the use of the list, see pages 164–167.
[b] For curative treatment.
[c] For prophylaxis.

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This guidance was discussed during two meetings convened by the Division of Drug Management and Policies and the Department of Essential Drugs and other Medicines, World Health Organization, Geneva, Switzerland, from 12 to 13 February 1996 and from 8 to 9 February 1999. The meetings were attended by the following people:

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Annex 12
Guidelines on the use of International Nonproprietary Names (INNs) for pharmaceutical substances

1. General introduction

The present guidelines on the use of International Nonproprietary Names (INNs) provide a general explanation of the INN selection process. They should be of interest to drug regulatory authorities for use in the marketing authorization/registration of products, to drug manufacturers requesting new INNs, and to those using INNs, such as patent authorities/offices, trademark lawyers and specialists, health professionals, scientists and teachers, as well as to anyone interested in nomenclature.

1.1 *General information on the INN system*

An INN identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.

The INN system as it exists today was initiated in 1950 by World Health Assembly resolution WHA3.11 (see section 5.1) and began operating in 1953, when the first list of INNs for pharmaceutical substances was published. The cumulative list of INNs now stands at some 7000 names designated since that time, and this number is growing every year by some 120–150 new INNs.

Since its inception, the aim of the INN system has been to provide health professionals with a unique and universally available designated name for each pharmaceutical substance. The existence of an international nomenclature for pharmaceutical substances, in the form of INNs, is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and the exchange of information among health professionals and scientists worldwide.

As unique names, INNs must be distinctive in sound and spelling, and not liable to confusion with other names in common use. To make INNs universally available, they are formally placed by WHO in the

public domain, hence their designation as "nonproprietary". They can be used without any restriction whatsoever to identify pharmaceutical substances.

Another important feature of the INN system is that the names of pharmacologically related substances were identified by the use of a common "stem" (see section 3.2). The use of common stems enables the medical practitioner, the pharmacist, or anyone dealing with pharmaceutical products to recognize that a particular substance belongs to a group of substances of similar pharmacological activity. For example, all iodine-containing contrast media are given the prefix io-, while all β-adrenoreceptor antagonists have the suffix -olol.

The extent of utilization of INNs is expanding with the increase in the number of pharmaceutical names. Their wide application and global recognition are also due to close collaboration in the process of INN selection with numerous bodies concerned with drug nomenclature. The increasing coverage of drug names by INNs has led to a situation whereby the majority of pharmaceutical substances used today in medical practice are designated by an INN. The use of INNs is already common in research and clinical documentation, while their importance is growing further as a result of the expanding use of generic names for pharmaceutical products.

The names which are given the status of an INN are selected by WHO on the advice of experts from the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The process of INN selection consists of three main steps:

1. A request/application is made by the manufacturer or inventor.
2. After a review of the request, a *proposed* INN (prop. INN) is selected and published for comments.
3. After the period allowed for objections has lapsed, the name obtains the status of a *recommended* INN (rec. INN) and is published as such.

The procedures relating to each of these steps are described in detail in sections 2.1 and 2.2.

INNs are selected in principle only for single, well-defined substances that can be unequivocally characterized by a chemical name (or formula). It is the policy of the INN programme not to select names for mixtures of substances, while substances that are not fully characterized are included in the INN system in exceptional cases only. INNs are not selected for herbal substances (vegetable drugs) or for

homeopathic products. It is also the policy of the INN programme not to select names for those substances that have a long history of use for medical purposes under well-established names, such as alkaloids (e.g. morphine, codeine), or that have well-known trivial chemical names (e.g. acetic acid).

An INN is usually assigned to the active part of the molecule only, to avoid the multiplication of entries in cases where several salts, esters, etc., are actually used. In such cases, the user of the INN can create a modified INN (INNM) (see section 2.4), e.g. mepyramine maleate for the mepyramine salt of maleic acid. When the creation of an INNM would require the use of a long or inconvenient name for the radical (or group) part of the INNM, the INN programme will select a short name for such a radical (or group) (e.g. mesilate for methanesulfonate; see section 2.3).

Names of pharmaceutical preparations, such as those used in titles of pharmacopoeial monographs, usually consist of two elements, the first designating the active substance (for which an INN is used), and the second designating the dosage form of the product. Rules for creating such names fall outside the scope of the INN programme and are not discussed here.

In the process of INN selection, the rights of existing trademark owners are fully protected. If, in a period of 4 months following the publication of a proposed INN, a formal objection is filed by an interested person who considers that the proposed INN is in conflict with an existing trademark, WHO will make every effort to persuade the person concerned to withdraw their objection or will reconsider the proposed name. As long as the objection to the name exists, WHO will not publish it as a recommended INN.

With the growing number of INNs and trademarks, the possibility of conflicts between the two has gradually increased, even though the rights of existing trademarks are fully protected. The main source of conflict is usually an attempt by a manufacturer to propose a new trademark containing stems established in the INN programme. If protection were granted to such a name, that might limit the freedom of the INN programme in selecting further INNs for the same group of substances. To prevent such occurrences, the matter was taken up in resolution WHA46.19 of the World Health Assembly (see section 4).

1.2 *Use of INNs*

Nonproprietary names are intended for use in pharmacopoeias, labelling, product information, advertising and other promotional

material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. Their use is normally required by national or, as in the case of the European Community, by international legislation. As a result of ongoing collaboration, national names such as British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN) and United States Accepted Names (USAN) are nowadays, with rare exceptions, identical to the corresponding INNs.

Some countries have defined the minimum size of characters in which the generic nonproprietary name must be printed under the trademark labelling and advertising. In several countries the generic name must appear prominently in type at least half the size of that used for the proprietary or brand name. In some countries it must be in larger type than the trademark name. Certain countries have even gone so far as to abolish trademarks within the public sector.

To avoid confusion, which could jeopardize the safety of patients, trademarks cannot be derived from INNs and, in particular, must not include their common stems. As already mentioned, the selection of further names within a group of substances would be seriously hindered by the use of a common stem in a brand name.

2. Elements in the INN system

2.1 *Proposed INNs*

The selection of a new INN follows a strict procedure. On receipt of an INN request form, the INN Secretariat examines the suggested names for conformity with the general rules, and for similarities with published INNs and potential conflicts with existing names, including published INNs and trademarks. A note summarizing the result of this examination is added, and the request is then forwarded to the INN experts for comments. As soon as all the experts agree on a name, the applicant is informed of the selected name.

Newly selected, proposed INNs are then published in *WHO Drug Information*, after which a period of 4 months is allowed for comments on and/or objections to them to be made. The reasons for any objection must be clearly stated and will be evaluated by the experts. Users are requested to refrain from using the proposed name until it becomes a recommended INN, in order to avoid confusion should the name be modified.

Two lists of proposed INNs are published yearly. An example is shown in Figure 1.

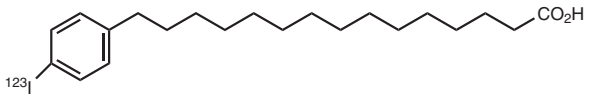
Figure 1
A proposed INN

acidum iocanlidicum (^{123}I)
iocanlidic (^{123}I) acid — 15-(*p*-[^{123}I]iodophenyl)pentadecanoic acid
radiodiagnostic agent

acide iocanlidique (^{123}I) — acide 15-(4-[^{123}I]iodophényl)pentadécanoïque
produit à usage radiodiagnostique

ácido iocanlídico (^{123}I) — ácido 15-(*p*-[^{123}I]iodofenil)pentadecanoico
agente de radiodiagnóstico

$C_{21}H_{33}{}^{123}IO_2$ 74855-17-7



2.2 *Recommended INNs*

The final stage of the selection process is the recommended INN. Once a name has been published as a recommended INN it will not normally be modified further and is ready for use in labelling, and in publications and drug information. It will serve to identify the active pharmaceutical substance during its lifetime worldwide. Since the name is available in the public domain it may be freely used. It should not be registered as a trademark, since this would prevent its use by other parties (see also section 4).

Recommended INNs are published in *WHO Drug Information* after the completion of the procedure for dealing with proposed INNs (see section 2.1). As from 1997, two lists of proposed INNs are published yearly, and as from list 37 of recommended INNs, graphic formulae are also included to facilitate identification of the substances.

An example of an entry in the list is shown in Figure 2.

2.3 *Names for radicals and groups*

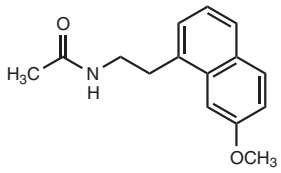
During the twentieth meeting of the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances (*1*), the experts discussed the issue of INNs for salts and esters and noted that requests had frequently been received for INNs for salts, esters, or combination products of substances for which INNs already existed. At that time, the experts decided that INNs for simple salts and esters should be derived from the INNs in conformity with normal chemical practice.

Figure 2
A recommended INN

agomelatinum

agomelatine	*N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide
agomélatine	*N*-[2-(7-méthoxynaphtalén-1-yl)éthyl]acétamide
agomelatina	*N*-[2-(7-metoxi-1-naftil)etil]acetamida

$C_{15}H_{17}NO_2$



Some of the radicals and groups involved are, however, so complex that it is inconvenient to use the chemical nomenclature. It was therefore decided that, in such cases, shorter nonproprietary names should be selected for these active moieties and published in the list of proposed INNs under the title "Names for radicals and groups". Separate names for salts and esters derived from this procedure are not published. If a "radical and group name" is used in conjunction with an INN, it is referred to as an International Nonproprietary Name (Modified) or INNM (see section 2.4).

A comprehensive list of radicals and groups, which is regularly updated, may be obtained from Marketing and Dissemination[1] or the INN Secretariat (*2*).

2.4 *Modified INNs (INNMs)*

As previously mentioned, INNs are usually selected only for the active part of the molecule, which is usually the base, acid or alcohol. In some cases, however, the active part needs to be extended for various reasons, e.g. for formulation purposes, or to increase the bioavailability or absorption rate of the substance. At its twentieth meeting in 1975, the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances (*1*) decided to adopt a new policy for naming such molecules. As a result, names for different

[1] Marketing and Dissemination, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland.

salts or esters of the same active substance should differ only with regard to the inactive moiety of the molecule. For example, oxacillin and ibufenac are INNs and their salts are named oxacillin sodium and ibufenac sodium. The latter are called modified INNs (INNMs).

Before the introduction of this rule, some INNs were published for salts. In such cases, the term "modified INN" may also be used for a base or acid. For example, levothyroxine sodium was published as an INN and levothyroxine may thus be referred to as an INNM.

2.5 *Cumulative list*

All names selected as proposed and recommended INNs are published in a cumulative list (*3*), which is updated periodically. The generic names are listed in alphabetical order by Latin name. Each entry includes:

— the equivalent nonproprietary names in Latin, English, French, Russian and Spanish;
— a reference to the INN list in which the name was originally proposed or recommended, or last amended;
— a reference to names of substances that have been abandoned or never marketed;
— a reference to national nonproprietary names;
— a reference to pharmacopoeial monographs or similar official publications;
— a reference to names established by the International Organization for Standardization (ISO);
— a reference to the Convention on Psychotropic Substances (*4*), if applicable;
— a reference to the List of Narcotic Drugs under International Control (*5*), if applicable;
— the molecular formula;
— the Chemical Abstracts Service (CAS) number.

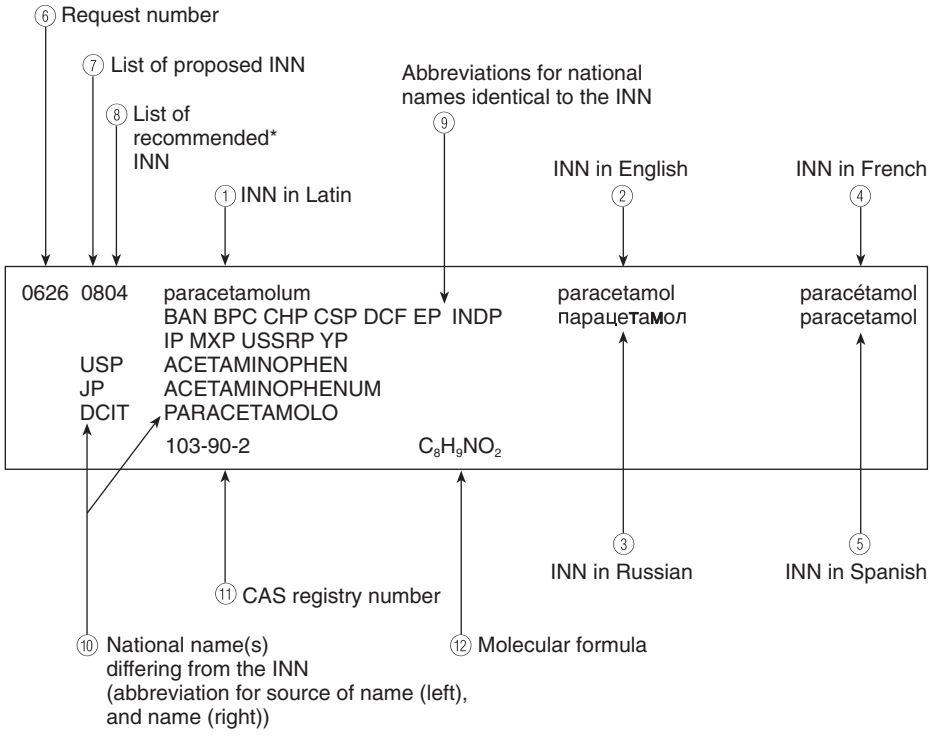
The information contained in the cumulative list of INNs (*3*) is presented as shown in Figure 3.

3. Principles for selection of INNs

3.1 *General rules*

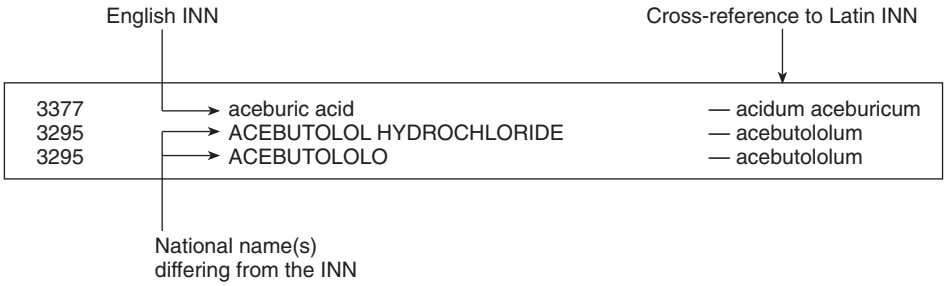
General rules were established at the beginning of the INN programme in order to guide the members of the INN committee and to allow health professionals to understand the rationale for a number of new names. At first, some countries used shortened chemical names as generic names, but this system was found to be of very limited use, since many molecules contain similar elements and

Figure 3
Example of an entry from the *Cumulative list*



* An asterisk in place of a recommended list number signifies that an objection has been raised to the proposed name.

Note: Cross-references are provided for entries corresponding to (a) English, French and Spanish INN that appear in different alphabetical positions from the Latin INN and (b) national names that differ from the INN. Entries for (a) are printed in lower-case letters (as in the example of aceburic acid, below) while entries for (b) are printed in capitals (as in the examples of ACEBUTOLOL HYDROCHLORIDE and ACEBUTOLOLO).



groups (e.g. phenol, chlor, methyl or benzene rings) in their chemical structures. In addition, a name that indicates a relationship to a group of substances having similar pharmacological effects is more meaningful to users.

The general principles for devising INNs and the procedures for selecting them were reviewed by the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances at its twentieth meeting (*1*).

3.2 *Use of stems*

An INN usually consists of a randomly chosen prefix and a common stem (see Appendix 1); the latter shows that the substance concerned belongs to a group of pharmacologically related substances. Substems are sometimes established to differentiate between different related groups of substances, e.g. -teplase for tissue-plasminogen activators and -uplase for urokinase-type plasminogen activators.

It should be noted that a number of stems have been discontinued (see Appendix 2).

3.3 *Stereoisomers*

An INN for a new chemical entity does not routinely specify the stereoisomeric state of the molecule in the nonproprietary name. If the stereochemistry has been determined, this information is included in the chemical name(s) used to identify the substance. An INN can therefore identify the racemic mixture (e.g. ibuprofen, tetramisole), the (–)-isomer (e.g. amifostine, lofentanil, prenalterol, remoxipride, quadazocine), or the (+)-form (e.g. butopamine). Subsequently, if an INN is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing INN:

— for the (–)-form, the lev-/levo- prefix is used, e.g. levocarnitine, levamisole;
— for the (+)-form, the dex- prefix is used, e.g. dexamisole, dexibuprofen;
— for the racemic form, the rac-/race- prefix is used, e.g. racepinefrine.

3.4 *Radioactive compounds*

A name for a drug substance containing a radioactive atom should list, in the following order:

— the name of the substance containing the radioactive atom;
— the isotope number;

— the element symbol; and
— the name of the carrier agent, if any.

Examples include cyanocobalamin (^{60}Co), technetium (^{99m}Tc) bicisate and technetium (^{99m}Tc) sestamibi.

3.5 *Specific groups of biological compounds*

Because of the complexity of certain new types of pharmaceutical products, such as those produced by biotechnology, general rules are not always easily formulated (*6*). Some of these substances may already have descriptive names assigned by other institutions such as the International Union of Biochemistry (IUB), the International Union of Pure and Applied Chemistry (IUPAC), and the Joint Commission on Biochemical Nomenclature (JCBN). These names may not be suitable as INNs.

4. Protection of INNs

Lists of both proposed and recommended INNs are sent together with a note verbale by WHO to its Member States (of which there are at present 191), to national pharmacopoeia commissions and to other bodies designated by Member States. The note verbale requests Member States to take such steps as are necessary to prevent the acquisition of proprietary rights in the names, including prohibiting their registration as tradenames or trademarks.

Over the years, the need to maintain the integrity of the INN system has become urgent. This is reflected in the following extract from the fifth report of the WHO Expert Committee on the Use of Essential Drugs (*7*), which met in November 1991:

> The procedure for selecting INNs allows manufacturers to contest names that are either identical or similar to their licensed trademarks. In contrast, trademark applications are disallowed, in accordance with the present procedure, only when they are identical to an INN. A case for increased protection of INNs is now apparent as a result of competitive promotion of products no longer protected by patents. Rather than marketing these products under the generic name, many companies apply for a trademark derived from an INN and, in particular, including the INN common stem. This practice endangers the principle that INNs are public property; it can frustrate the rational selection of further INNs for related substances, and it will ultimately compromise the safety of patients by promoting confusion in drug nomenclature.

These concerns were debated during the Sixth International Conference of Drug Regulatory Authorities (ICDRA) in Ottawa in October 1991.

On the basis of the recommendations made by the WHO Expert Committee on the use of Essential Drugs, a resolution on nonproprietary names for pharmaceuticals (WHA46.19) was adopted by the World Health Assembly in 1993 (*8*). This requested Member States:

- to enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic names) used in the labelling and advertising of pharmaceutical products are always displayed prominently;
- to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than on trademarks, to promote and market multisource products introduced after the expiry of a patent;
- to develop policy guidelines on the use and protection of international nonproprietary names, and to discourage the use of names derived from them, and particularly names including established stems as trademarks.

Attention is drawn to this resolution concerning the use and protection of INNs in the note verbale.

As a matter of principle, it may thus be recommended that trademarks should not be derived from INNs. In particular, the intentional incorporation of meaningful INN stems in trademarks should be avoided.

Similarly, the inclusion of elements from biochemical nomenclature (e.g. -feron from interferon, or -leukin from interleukin) in trademarks is discouraged since these elements are likely to be used as stems within the INN nomenclature. Their inclusion in trademarks could thus prevent the logical development of the INN nomenclature.

In accordance with resolution WHA46.19, the registration of an INN together with a firm's name is perfectly acceptable as long as it does not prevent another manufacturer from adopting the same approach.

5. How to apply for an INN

5.1 *Procedure for selection of INNs*

The selection of INNs is based on the resolution on the procedure for the selection of INNs for pharmaceutical substances (WHA3.11) adopted by the World Health Assembly in 1950 (*9*), and subsequently adopted and amended by the Executive Board in 1955 (*10*) and 1969 (*11*).

In countries with national nomenclature commissions, applications for INNs can be made through these commissions. In countries without a national nomenclature commission, requests for INNs may be forwarded directly to WHO. Applications for INNs should be addressed to:

Secretary of the INN Programme
Quality Assurance and Safety: Medicines
Essential Drugs and Medicines Policy
World Health Organization
20 avenue Appia
1211 Geneva 27
Switzerland
Tel: +41 22 791 0746
Fax: +41 22 791 3636/3660

5.2 *INN request form*

Before a suggested name can be evaluated by the INN Secretariat, complete information must be provided on a request form to facilitate handling of the data and to ensure that pertinent items have not been omitted. It is important that the information is as comprehensive as possible. If some of the information is missing or explanations are unclear or incomplete, the INN Secretariat will request the applicant to provide the missing data or further explanation. This can result in delays, because an INN cannot be selected until all the relevant information is available to the INN experts.

The following explanations will help applicants to complete the INN form. If additional information is needed, an applicant can contact the INN Secretariat at the above-mentioned address.

Suggested names in order of preference

An applicant can suggest three names for an INN relating to the acid, base or alcohol of the chemical entity concerned. The suggested name should be a single word and not inconveniently long.

Since a nonproprietary name is intended to show the group of pharmacologically related substances to which the substance concerned belongs, whenever justified, the suggested name must incorporate the established common stem. A list of stems (*12*) is available on request from Marketing and Dissemination[1] or the INN Secretariat.

Occasionally stems require modification. For example, some drugs inhibit α-adrenoreceptors as well as β-adrenoreceptors and differ in structure from the "-olol" prototype. Accordingly, for this type of drug, one letter in the stem was changed to give "-alol". The significance of this change in the naming of related groups of drugs might

[1] Marketing and Dissemination, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland.

not be apparent to everyone, but would be understood by someone familiar with the naming conventions of the β-adrenoreceptor antagonists and related compounds.

It is imperative that the newly suggested name does not conflict with existing chemical names, other nonproprietary names or trademarks. The INN Secretariat therefore requests the applicant to verify the absence of conflicts with existing chemical names, common names for insecticides, other nonproprietary names and trademarks. Some firms routinely perform exhaustive searches for possible conflicts with a suggested INN and for pharmacologically and chemically related compounds with already assigned INNs. It would be helpful if the INN Secretariat could be informed when such searches have been carried out and be given a summary of the results.

Chemical name and description

The chemical information provided on the request form should be as complete and as up to date as possible. Information on stereochemistry should be included, if known. The chemical names should be in accordance with the IUPAC rules of nomenclature, as interpreted by the Chemical Abstracts Service (CAS) (8th collective period); the Chemical Abstracts Index names in their current style may also be included as additional information. The chemical name provided by the manufacturer is reviewed for accuracy and to confirm that its construction follows the accepted rules of chemical nomenclature.

A description can be used to identify a substance that is insufficiently defined to be assigned a IUPAC and CAS chemical name. This description will be superseded by the chemical name when the drug substance has been fully characterized.

Precautions are taken to ensure confidentiality of the material submitted to WHO, but an applicant should not attempt to obtain an INN before all patent procedures are completed and until full chemical information can be made available to WHO.

Graphic formula

Without a graphic formula, it may be difficult to determine whether an INN already exists. In addition, a graphic formula is necessary to relate the new drug to existing compounds in the same chemical family. Guidelines for drawing structures are available on request from the INN Secretariat (*13*).

Molecular formula

A one-line molecular formula constructed in accordance with accepted chemical practices should be supplied, e.g. $C_{21}H_{28}N_2$.

CAS registry number

If a CAS registry number has been assigned to a new compound before it is submitted to the INN Secretariat, the number should be included on the request form. If no number has yet been assigned, the manufacturer should obtain the CAS registry number from the Chemical Abstracts Services for publication in the INN lists. Proof of the entry will be required.

Trademarks (known or contemplated)

If a trademark has been issued for the drug, it should be entered on the form. Any national or international trademarks (and manufacturers) and the name of the country where the trademark is registered should be listed.

Any other name or code

Sometimes, long before a nonproprietary name or a trademark has been selected for a new compound, it may have acquired a trivial name that has been used both in the laboratory and in the scientific literature. The INN Secretariat would like to be made aware of such names but requests manufacturers not to create, use or in any way encourage the creation of trivial names for new drugs. The fact that a trivial name has become accepted in the literature will not ensure its adoption as a nonproprietary name and may only cause confusion when an official nonproprietary name is selected. It is therefore recommended that codes should be used before a recommended nonproprietary name is published, and that these should be indicated on the request form sent to the INN Secretariat as an additional reference.

Principal therapeutic use(s) and posology

It is important to know the therapeutic category to which the new compound belongs as such information may determine the stem selected for the nonproprietary name. Reprints presenting evidence of the claimed therapeutic use should be included with the application. A list of terms for the pharmacological action and therapeutic use of drugs is available from WHO in English, French and Spanish (*14*).

Pharmacological action

The pharmacological action should be explained in as much detail as possible, since it may also influence the stem selected for the compound. Again, reprints must be included to support the claimed action (for terminology, see above).

Date of clinical trial

As a general guide, the development of a drug should have reached the stage of phase II clinical trials before an application is submitted

to the INN Secretariat. The approximate date when clinical trials began should be indicated as proof that such trials are under way. It is the belief that if a drug has entered clinical trials, there is a reasonable expectation that it will be marketed, and thus the name selected will have been developed for that purpose. If, however, the development of the drug is stopped, the manufacturer should inform the INN Secretariat as soon as possible, in order to halt the selection process.

Availability of suggested names
The originator of the INN request should confirm with his or her signature that the names are suggested on the understanding that, so far as is known, none of them have been registered or are awaiting registration.

Permission to publish the CAS registry number
The applicant must confirm that the CAS registry number sent to the INN Secretariat is correct and may be used in the INN lists.

Additional comments
This section allows the applicant to make additional comments and/or provide further information.

References

1. *Nonproprietary names for pharmaceutical substances. Twentieth report of the WHO Expert Committee*. Geneva, World Health Organization, 1975 (WHO Technical Report Series, No. 581).
2. *INNs: names for radicals and groups, combined summary list*.[1] Geneva, World Health Organization (unpublished document WHO/PHARM S/NOM1506; available from INN Secretariat, Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).
3. *International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 9*. Geneva World Health Organization, 1996.
4. *Convention on Psychotropic Substances, 1971*. Vienna, United Nations, 1978.
5. *List of narcotic drugs under international control*, 41st ed. Vienna, United Nations, 1999.
6. *Definition of INNs for substances prepared by biotechnology*.[1] Geneva, World Health Organization (unpublished document WHO/PHARM S/NOM1348; available from INN Secretariat, Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).
7. *The use of essential drugs. Fifth report of the WHO Expert Committee*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 825).

[1] Updated regularly.

8. Nonproprietary names for pharmaceutical substances. In: *Forty-sixth World Health Assembly, Geneva, 3–14 May 1993. Volume 1. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1993 (unpublished document WHA46/1993/REC/1):20–21.

9. Nonproprietary names for pharmaceutical substances. In: *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board. Volume I, 1948–1972*. Geneva, World Health Organization, 1973:128.

10. EB15.R1. In: *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board. Volume I, 1948–1972*. Geneva, World Health Organization, 1973:129.

11. EB43.R9. In: *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board. Volume I, 1948–1972*. Geneva, World Health Organization, 1973:130.

12. *The use of common stems in the selection of international nonproprietary names (INNs) for pharmaceutical substances*. Geneva, World Health Organization (unpublished document updated annually; available from INN Secretariat, Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).

13. *The graphic representation of chemical formulae in the publications of international nonproprietary names (INNs) for pharmaceutical substances*. Geneva, World Health Organization, 1995 (unpublished document WHO/PHARM/95.579; available from INN Secretariat, Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).

14. *Pharmacological action and therapeutic use of drugs: a list of terms.* Geneva, World Health Organization, 1996 (unpublished document WHO/PHARM/96.320; available from Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).

Appendix 1
List of common stems used in the selection of INNs

Stem[a]	Substem, if available	Definition
-abine		*see* -arabine, -citabine
-ac		anti-inflammatory agents, ibufenac derivatives
-acetam		*see* -racetam
-actide		synthetic polypeptides with corticotropin-like action
-adol or -adol-		analgesics
-adom		analgesics, tifluadom derivatives
-afenone		antiarrhythmics, propafenone derivatives
-aj-		antiarrhythmics, ajmaline derivatives
-aldrate		antacids, aluminium salts
-alol		*see* -olol
-alox		*see* -ox
-amab		*see* -mab
-amivir		*see* vir
andr		steroids, androgens (*see also* -stan- or -ster-)
-anide		
	-etanide	diuretics, piretanide derivatives
	-oxanide	antiparasitic, salicylanilides and analogues
-anserin		serotonin receptor antagonists (mostly 5-HT_2)
-antel		anthelminthics (undefined group)
-apine		*see* -pin(e)
-a(ra)bine		arabinofuranosyl derivatives
-arit		antiarthritic substances, with a similar mechanism of action to clobuzarit and lobenzarit (mechanism different from anti-inflammatory-type substances, e.g. -fenamates or -profens)
-arol		anticoagulants, dicoumarol derivatives
-arone		antiarrhythmics, calcium channel blockers, uricosurics
-arte-		antimalarial agents, artemisinin-related compounds
-ase		enzymes:
	-diplase	— plasminogen activator combined with another enzyme
	-dismase	— with superoxide dismutase activity
	-lipase	— with lipase activity
	-teplase	— tissue-type plasminogen activators
	-uplase	— urokinase-type plasminogen activators
-ast		antiasthmatics, antiallergics, not acting primarily as antihistamines:
	-lukast	— leukotriene receptor antagonists (*see also* -lubant)

Stem[a]	Substem, if available	Definition
	-trodast	— thromboxane A_2 receptor antagonists, antiasthmatics
-asteride		*see* -ster
-astine		antihistamines
-azam		*see* -azepam
-azenil		benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives):
	-carnil	— benzodiazepine receptor antagonists/agonists (carboline derivatives)
	-quinil	— benzodiazepine receptor partial agonists (quinoline derivatives)
-azepam		diazepam derivatives
-azepide		cholecystokinin receptor antagonists
-azocine		narcotic antagonists/agonists related to 6,7-benzomorphan
-azolam		*see* -azepam
-azoline		antihistamines or local vasoconstrictors, antazoline derivatives
-azone		*see* -buzone
-azosin		antihypertensive substances, prazosin derivatives
-bactam		β-lactamase inhibitors
-bamate		tranquillizers, propanediol and pentanediol derivatives
barb		hypnotics, barbituric acid derivatives
-benakin		*see* -kin
-bendan		*see* -dan
-bendazole		anthelminthics, tiabendazole derivatives
-betasol		*see* pred
bol		anabolic steroids
-bradine		bradycardic agents
-brate		*see* -fibrate
-butazone		*see* -buzone
-buzone		anti-inflammatory analgesics, phenylbutazone derivatives
-cain-		class I antiarrhythmics, procainamide and lidocaine derivatives (antifibrillants with local anaesthetic activity)
-caine		local anaesthetics
calci		vitamin D analogues/derivatives
-carbef		antibiotics, carbacephem derivatives
-carnil		*see* -azenil
-castat		*see* -stat
-cavir		*see* vir
cef-		antibiotics, cefalosporanic acid derivatives:
	-oxef	— antibiotics, oxacefalosporanic acid derivatives
cell-, -cell- or cel-		cellulose derivatives:

Stem[a]	Substem, if available	Definition
	cell-ate	— cellulose ester derivatives for substances containing acidic residues
	-cellose	— cellulose ether derivatives
cell-ate		*see* cell-
-cellose		*see* cell-
-cic		hepatoprotective substances with a carboxylic acid group
-cidin		naturally occurring antibiotics (undefined group)
-cillide		*see* -cillin
-cillin		antibiotics, 6-aminopenicillanic acid derivatives
-cillinam		*see* -cillin
-cilpine		*see* -pin(e)
-cisteine		*see* -steine
-citabine		nucleoside antiviral or antineoplastic agents, cytarabine or azarabine derivatives
-clone		hypnotic tranquillizers
-cog		blood coagulation factors:
	(-)eptacog	— blood coagulation factor VII
	(-)nonacog	— blood coagulation factor IX
	(-)octacog	— blood coagulation factor VIII
-conazole		systemic antifungal agents, miconazole derivatives
cort		corticosteroids, except prednisolone derivatives
-crinat		diuretics, etacrynic acid derivatives
-crine		acridine derivatives
-cromil		antiallergics, cromoglicic acid derivatives
-curium		*see* -ium
-cycline		antibiotics, tetracycline derivatives
-dan		cardiac stimulants, pimobendan derivatives
-dapsone		antimycobacterials, diaminodiphenylsulfone derivatives
-decakin		*see* -kin
-dermin		*see* -ermin
-dil		vasodilators
-dilol		*see* -dil
-dipine		calcium channel blockers, nifedipine derivatives
-dismase		*see* -ase
-distim		*see* -stim
-dodekin		*see* -kin
-dopa		dopamine receptor agonists, dopamine derivatives, used as antiparkinsonism drugs/prolactin inhibitors:
	-opamine	— dopaminergic agents, dopamine derivatives used as cardiac stimulants/antihypertensives/diuretics
-dox		*see* -ox
-dralazine		antihypertensives, hydrazinephthalazine derivatives

Stem[a]	Substem, if available	Definition
-drine		sympathomimetics:
	-frine	— phenethyl derivatives
-dronic acid		calcium metabolism regulator, pharmaceutical adjunct
-dutant		*see* -tant
-dyl		*see* -dil
-ectin		antiparasitics, ivermectin derivatives
-elestat		*see* -stat
-elvekin		*see* -kin
-emab		*see* -mab
-entan		endothelin receptor antagonists
-eptacog		*see* -cog
erg		ergot alkaloid derivatives
-eridine		analgesics, pethidine derivatives
-ermin		growth factors:
	-dermin	— epidermal growth factors
	-fermin	— fibrinoblast growth factors
	-filermin	— leukaemia-inhibiting factor
	-nermin	— tumour necrosis factor
	-plermin	— platelet-derived growth factor
	-sermin	— insulin-like growth factors
	-termin	— transforming growth factor
estr-		estrogens
-etanide		*see* -anide
-ethidine		*see* -eridine
-exakin		*see* -kin
-exine		mucolytic, bromhexine derivatives
-fenamic acid		anti-inflammatory, anthranilic acid derivatives
	-fenamate	— fenamic acid derivatives
-fenin		diagnostic aids, (phenylcarbamoyl)methyl iminodiacetic acid derivatives
-fenine		analgesics, glafenine derivatives (subgroup of -fenamic acid group)
-fentanil		narcotic analgesics, fentanyl derivatives
-fermin		*see* -ermin
-fiban		fibrinogen receptor antagonists (glycoprotein IIb/IIIa receptor antagonists)
-fibrate		clofibrate derivatives
-filermin		*see* -ermin
-flapon		5-lipoxygenase-activating protein (FLAP) inhibitor
-flurane		halogenated compounds used as general inhalation anaesthetics
-formin		antihyperglycaemics, phenformin derivatives
-fos, -fos- or fos-		insecticides, anthelminthics, pesticides, etc., phosphorus derivatives
-fradil		calcium channel blockers acting as vasodilators
-frine		*see* -drine
-fungin		antifungal antibiotics

Stem[a]	Substem, if available	Definition
-fylline		*N*-methylated xanthine derivatives
gab		gabamimetic agents
gado-		diagnostic agents, gadolinium derivatives
-gatran		thrombin inhibitors, antithrombotic agents
gest		steroids, progestogens
-gesterone		*see* -ster
-giline		monoamine oxidase inhibitors, type B
-gillin		antibiotics produced by *Aspergillus* spp.
gli		antihyperglycaemics, sulfonamide derivatives
-golide		dopamine receptor agonists, ergoline derivatives
-gosivir		*see* vir
-gramostim		*see* -stim
-grastim		*see* -stim
-grel- or -grel		platelet aggregation inhibitors
guan-		antihypertensives, guanidine derivatives
-ibine		*see* -ribine
-icam		anti-inflammatory, isoxicam derivatives
-ifene		antiestrogens, clomifene and tamoxifen derivatives
-igetide		*see* -tide
-ilide		class III antiarrhythmics, sematilide derivatives
-imab		*see* -mab
imex		immunostimulants
-imod		immunomodulators, both stimulant/suppressive and stimulant
-imus		immunosuppressants (other than antineoplastics)
-ine		alkaloids and organic bases
io-		iodine-containing contrast media
-io- or iod-		iodine-containing compounds other than contrast media
-iptan		serotonin ($5HT_1$) receptor agonists, sumatriptan derivatives
-irudin		hirudin derivatives
-isomide		antiarrhythmics, disopyramide derivatives
-ium		quaternary ammonium compounds:
	-curium	— curare-like substances
-izine		diphenylmethyl piperazine derivatives:
	-rizine	— antihistamines/cerebral (or peripheral) vasodilators
-kacin		antibiotics, kanamycin and bekanamycin derivatives (obtained from *Streptomyces kanamyceticus*)
-kalant		potassium channel blockers
-kalim		potassium channel activators, antihypertensive
-kef-		enkephalin agonists
-kin		interleukin (IL)-type substances (*see also* -stim):
	-benakin	— IL-1β analogues and derivatives

Stem[a]	Substem, if available	Definition
	-decakin	— IL-10 analogues and derivatives
	-dodekin	— IL-12 analogues and derivatives
	-elvekin	— IL-11 analogues and derivatives
	-exakin	— IL-6 analogues and derivatives
	-kinra	— IL receptor antagonists
	-leukin	— IL-2 analogues and derivatives
	-nakin	— IL-1 analogues and derivatives
	-nakinra	— IL-1 receptor antagonists
	-octakin	— IL-8 analogues and derivatives
	-onakin	— IL-1α analogues and derivatives
	-trakin	— Il-4 analogues and derivatives
-kinra		*see* -kin
-kiren		renin inhibitors
-leukin		*see* -kin
-listat		*see* -stat
-lubant		leukotriene B_4 receptor antagonist (*see also* -ast)
-lukast		*see* -ast
-mab		monoclonal antibodies:
	-amab	— of rat origin
	-emab	— of hamster origin
	-imab	— of primate origin
	-omab	— of mouse origin
	-umab	— of human origin
	-ximab	— of chimeric origin
	-zumab	— of humanized origin
-mantadine, -mantine or -mantone		adamantane derivatives
-meline		cholinergic agents, muscarinic receptor agonists/partial antagonists used in the treatment of Alzheimer disease
-mer		polymers
-mesine		sigma receptor ligands
-mestane		aromatase inhibitors
-metacin		anti-inflammatory, indometacin derivatives
-met(h)asone		*see* pred
-micin		antibiotics obtained from various *Micromonospora* spp.
-mifene		*see* -ifene
-monam		monobactam antibiotics
-morelin		*see* -relin
-mostim		*see* -stim
-motine		antivirals, quinoline derivatives
-moxin		monoamine oxidase inhibitors, hydrazine derivatives
-mustine		antineoplastic, alkylating agents, (β-chloroethyl)amine derivatives
-mycin		antibiotics obtained from various *Streptomyces* spp. (*see also* -kacin)

Stem[a]	Substem, if available	Definition
nab		cannabinol derivatives
-nakin		*see* -kin
-nakinra		*see* -kin
nal-		narcotic antagonists/agonists related to normorphine
-naritide		*see* -tide
-navir		*see* vir
-nercept		tumour necrosis factor antagonist
-nermin		*see* -ermin
-netant		*see* -tant
-nicate		*see* nico-
nico-, nic- or ni-		nicotinic acid or nicotinoyl alcohol derivatives:
	-nicate	— antihypercholesterolaemic and/or vasodilating nicotinic acid esters
-nidazole		antiprotozoals, metronidazole derivatives
-nidine		*see* -onidine
nifur-		5-nitrofuran derivatives
-nil		*see* -azenil
nitro-, nitr-, nit-, ni- or -ni-		NO_{2-} derivatives
-nixin		anti-inflammatory, anilinonicotinic acid derivatives
-nonacog		*see* -cog
-octacog		*see* -cog
-octakin		*see* -kin
-olol		β-adrenoreceptor antagonists:
	-alol	— aromatic ring –CHOH–CH_2–NH–R related to -olols
-olone		*see* pred
-omab		*see* -mab
-onakin		*see* -kin
-one		ketones
-onide		steroids for topical use, acetal derivatives
-onidine		antihypertensives, clonidine derivatives
-onium		*see* -ium
-opamine		*see* -dopa
-orex		anorectics
-orph-		*see* orphan
orphan		narcotic antagonists/agonists, morphinan derivatives
-ox		antacids, aluminium derivatives:
	-pirox	— antimycotic pyridone derivatives
	-xanox	— antiallergics, tixanox group
-oxacin		antibacterials, nalidixic acid derivatives
-oxan(e)		benzodioxane derivatives
-oxanide		*see* -anide
-oxef		*see* cef-
-oxepine		*see* -pine
-oxetine		antidepressants, fluoxetine derivatives

Stem[a]	Substem, if available	Definition
-oxicam		*see* -icam
-oxifene		*see* -ifene
-oxopine		*see* -pine
-pafant		platelet-activating factor antagonists
-pamide		diuretics, sulfamoylbenzoic acid derivatives
-pamil		coronary vasodilators, verapamil derivatives
-parcin		glycopeptide antibiotics
-parin		heparin derivatives including those of low relative molecular mass:
	-parinux	— synthetic heparinoids
-parinux		*see* -parin
-pase		*see* -ase
-pendyl		*see* -dil
-penem		analogues of penicillanic acid antibiotics modified in the five-membered ring
perfl(u)-		perfluorinated compounds used as blood substrates and/or diagnostic agents
-peridol		*see* -perone
-peridone		*see* -perone
-perone		tranquillizers, neuroleptics, 4′-fluoro-4-piperidinobutyrophenone derivatives:
	-peridol	— antipsychotics, haloperidol derivatives
	-peridone	— antipsychotics, risperidone derivatives
-phenine		*see* -fenine
-pidem		hypnotics/sedatives, zolpidem derivatives
-pin(e)		tricyclic compounds:
	-apine	— psychoactive
	-cilpine	— antiepileptic
	-zepine	— antidepressant/neuroleptic
-piprazole		*see* -prazole
-pirone		*see* -spirone
-pirox		*see* -ox
-pitant		*see* -tant
-plact		platelet factor 4 analogues and derivatives
-planin		antibacterials obtained from various *Actinoplanes* spp.
-plase		*see* -ase
-platin		antineoplastic agents, platinum derivatives
-plermin		*see* -ermin
-plestim		*see* -stim
-plon		pyrazolo[.]pyrimidine derivatives, used as anxiolytics, sedatives, hypnotics
-poetin		erythropoietin-type blood factors
-porfin		benzoporphyrin derivatives
-poride		Na^+/H^+ antiport inhibitor
-pramine		substances of the imipramine group
-prazole		antiulcer, benzimidazole derivatives:
	-piprazole	— psychotropics, phenylpiperazine derivatives
pred		prednisone and prednisolone derivatives:

Stem[a]	Substem, if available	Definition
	-olone	— steroids other than prednisolone derivatives
-prenaline		*see* -terol
-pressin		vasoconstrictors, vasopressin derivatives
-pride		sulpiride derivatives
-pril(at)		angiotensin-converting enzyme inhibitors
-prim		antibacterials, trimethoprim derivatives
-profen		anti-inflammatory agents, ibuprofen derivatives
prost		prostaglandins:
	-prostil	— anti-ulcer
-prostil		*see* prost
-quinil		*see* -azenil
-racetam		amide-type nootrope agents, piracetam derivatives
-relin		prehormones or hormone release-stimulating peptides:
	-morelin	— growth hormone release-stimulating peptides
	-tirelin	— thyrotropin-releasing hormone analogues
-relix		hormone release-inhibiting peptides
-renone		aldosterone antagonists, spironolactone derivatives
-restat or -restat-		*see* -stat
retin		retinol derivatives
-ribine		ribofuranyl derivatives of the "pyrazofurin" type
rifa-		antibiotics, rifamycin derivatives
-rinone		cardiac stimulants, amrinone derivatives
-rizine		*see* -izine
-rozole		aromatase inhibitors, imidazole–triazole derivatives
-rubicin		antineoplastic antibiotics, daunorubicin derivatives
sal-, -sal or -sal-		analgesic, anti-inflammatory salicylic acid derivatives:
	-salan	— brominated salicylamide derivatives, disinfectant
	-salazo	— phenylazosalicylic acid derivatives, antibacterial
-salan		*see* sal-
-salazine or -salazide		*see* sal-
-salazo		*see* sal-
-sartan		angiotensin II receptor antagonists, antihypertensive (non-peptidic)
-semide		diuretics, furosemide derivatives
-sermin		*see* -ermin
-serpine		derivatives of *Rauwolfia* alkaloids
-setron		serotonin receptor antagonists (5-HT_3) not fitting into other established groups of serotonin receptor antagonists

Stem[a]	Substem, if available	Definition
som-		growth hormone derivatives
-sopine		*see* -pin(e)
-spirone		anxiolytics, buspirone derivatives
-stat or -stat-		enzyme inhibitors:
	-castat	— dopamine β-hydroxylase inhibitors
	-elestat	— elastase inhibitors
	-listat	— pancreatic lipase inhibitors
	-mastat	— matrix metalloproteinase inhibitors
	-restat or -restat-	— aldose reductase inhibitors
	-vastatin	— antilipidaemic substances, HMG CoA reductase inhibitors
-steine		mucolytics, other than bromhexine derivatives
-ster-		androgens/anabolic steroids:
	-(a)steride	— antineoplastics
-stigmine		acetylcholinesterase inhibitors
-stim		colony-stimulating factors:
	-distim	— combination of two different types of colony-stimulating factor
	-gramostim	— granulocyte macrophage colony-stimulating factor (GM-CSF)-type substances
	-grastim	— granulocyte colony-stimulating factor (G-CSF)-type substances
	-mostim	— macrophage colony-stimulating factor (M-CSF)-type substances
	-plestim	— IL-3 analogues and derivatives
sulfa-		anti-infectives, sulfonamides
-sulfan		antineoplastics, alkylating agents, methanesulfonates
-tant		neurokinin (tachykinin) receptor antagonists:
	-dutant	— neurokinin NK_2 receptor antagonist
	-netant	— neurokinin NK_3 receptor antagonist
	-pitant	— neurokinin NK_1 (substance P) receptor antagonist
-tecan		antineoplastics, topoisomerase I inhibitors
-tepa		antineoplastics, thiotepa derivatives
-tepine		*see* -pin(e)
-teplase		*see* -ase
-terenol		*see* -terol
-termin		*see* -ermin
-terol		bronchodilators, phenylethylamine derivatives
-terone		antiandrogens
-tiazem		calcium channel blockers, diltiazem derivatives
-tide		peptides and glycopeptides (for specific groups of peptides, *see* -actide, -pressin, -relin and -tocin)
-tidine		histamine H_2 receptor antagonists, cimetidine derivatives
-tiline		*see* -triptyline
-tirelin		*see* -relin

Stem[a]	Substem, if available	Definition
-tizide		diuretics, chlorothiazide derivatives
-tocin		oxytocin derivatives
-toin		antiepileptics, hydrantoin derivatives
-trakin		*see* -kin
-trexate		folic acid analogues
-tricin		antibiotics, polyene derivatives
-triptan		serotonin ($5HT_1$) receptor agonists, sumatriptan derivatives
-triptyline		antidepressants, dibenzo[*a*,*d*]cycloheptane or cycloheptene derivatives
-troban		thromboxane A_2 receptor antagonists, antithrombotic agents
-trodast		*see* -ast
trop		atropine derivatives
-umab		*see* -mab
-uplase		*see* -ase
-ur		*see* -uridine
-uracil		uracil derivatives used as thyroid antagonists and as antineoplastics
-uridine		uridine derivatives used as antiviral agents and as antineoplastics:
	-vudine	— zidovudine-type antivirals and antineoplastics
-vastatin		*see* -stat
-verine		spasmolytics with a papaverine-like action
vin- or -vin-		vinca alkaloids
vir		antivirals (undefined group):
	-amivir	— neuraminidase inhibitors
	-cavir	— carbocyclic nucleosides
	-gosivir	— glucoside inhibitors
	-navir	— HIV protease inhibitors
-virsen		antisense oligonucleotides
-vos		*see* -fos
-vudine		*see* -uridine
-xanox		*see* -ox
-ximab		*see* -mab
-yzine		*see* -izine
-zafone		alozafone derivatives
-zepine		*see* -pin(e)
-zone		*see* -buzone
-zumab		*see* -mab

[a] The hyphens indicate the position of the stem (prefix, infix or suffix) within the INN. If the hyphen is absent, the stem may be used in any position within the name.

Appendix 2
Common stems that have been discontinued

Stem[a]	Definition
-al(d)	aldehydes (deleted from General Principles in 14th report of the WHO Subcommittee on Nonproprietary Names (1968))
mer- or -mer-	mercury-containing drugs, antimicrobial or diuretic (deleted from General Principles in List 28 of proposed INNs)
mito-	antineoplastics, nucleotoxic agents (deleted from General Principles in List 24 of proposed INNs)
-ol	alcohols and phenols (deleted from General Principles in 14th report of the WHO Subcommittee on Nonproprietary Names (1968))
-quine or quin	quinoline derivatives (deleted from General Principles in List 28 of proposed INNs)

[a] The hyphens indicate the position of the stem (prefix, infix or suffix) within the INN. If the hyphen is absent, the stem may be used in any position within the name.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The international pharmacopoeia, third edition.
Volume 1: general methods of analysis. 1979 (223 pages)
Volume 2: quality specifications. 1981 (342 pages)
Volume 3: quality specifications. 1988 (407 pages)
Volume 4: tests, methods, and general requirements: quality specifications for pharmaceutical substances, excipients and dosage forms. 1994 (358 pages)

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms.
1998 (94 pages)

Basic tests for pharmaceutical dosage forms.
1991 (134 pages)

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials.
Volume 1: 1997 (244 pages)
Volume 2: good manufacturing practices and inspection. 1999 (201 pages)

Quality control methods for medicinal plant materials.
1998 (123 pages)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.
Thirty-fifth report.
WHO Technical Report Series, No. 885, 1999 (162 pages)

International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 9.
1996 (898 pages)

The use of essential drugs.
Ninth report of the WHO Expert Committee (including the revised Model List of Essential Drugs).
WHO Technical Report Series, No. 895, 2000 (66 pages)

WHO Expert Committee on Biological Standardization.
Forty-eighth report.
WHO Technical Report Series, No. 889, 1999 (117 pages)

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This report presents the recommendations of an international group of experts convened by the World Health Organization to consider matters concerning the quality assurance of pharmaceuticals and specifications for drug substances and dosage forms. Of particular relevance to drug regulatory authorities and pharmaceutical manufacturers, the report discusses activities related to the development of *The international pharmacopoeia* and basic tests for pharmaceutical substances and dosage forms, as well as quality control of reference materials, good manufacturing practices (GMP), packaging and other aspects of quality assurance of pharmaceuticals, nomenclature and regulatory issues.

The report is complemented by numerous annexes, including lists of available International Chemical Reference Substances and International Infrared Reference Spectra, considerations for requesting analysis of drug samples, guidelines on pre-approval inspections of pharmaceutical manufacturers, and guidelines for packaging of pharmaceutical products. Guidance is provided on the basic elements of GMP and the requirements for sterile products and for national GMP inspectorates of pharmaceutical manufacturers. The final annexes provide guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products and the use of International Nonproprietary Names (INNs).

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