WHO Expert Committee on Specifications for Pharmaceutical Preparations

Thirty-first Report

World Health Organization
Technical Report Series
790

World Health Organization, Geneva 1990
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PHARMACEUTICAL PREPARATIONS

Geneva, 28 November–3 December 1988

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WHO EXPERT COMMITTEE ON
SPECIFICATIONS FOR
PHARMACEUTICAL PREPARATIONS

Thirty-first Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 28 November to 3 December 1988. The meeting was opened on behalf of the Director-General by Dr V. Fattorusso, Adviser to Dr Hu Ching-Li, Assistant Director-General, who recalled that the supply of good-quality essential drugs—identified at the International Conference on Primary Health Care, Alma-Ata, 1978, as one of the basic prerequisites for the delivery of health care—had long been of fundamental concern to the World Health Organization. Pivotal to its efforts in this connection had been the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. However, rigorous procedures for attesting the quality and provenance of imported products needed to be complemented, wherever possible, by the analytical facilities afforded by a national drug quality-control laboratory and, above all, by a reliable system of licensing pharmaceutical products as a prerequisite for their distribution and sale. For this reason, emphasis had been accorded within WHO’s revised drug strategy to the need to prepare guiding principles for small national drug regulatory authorities. The Committee was consequently requested to consider, in addition to various important technical issues relating to quality assurance, some draft guidelines addressing this need that had been prepared as a consultative document and to submit any recommendations it might care to propose to the Director-General.

1. DRUG STABILITY

Inadequate storage and distribution of pharmaceutical products can lead to their physical deterioration and chemical decomposition, resulting in reduced activity and, occasionally, in the formation of toxic degradation products. Degradation is particularly likely to occur under tropical conditions of high ambient temperature and
humidity; and it is not widely recognized that, because of the potential for chemical interaction between the active ingredients and excipients, drug dosage forms can be more vulnerable to degradation than pure drug substances.

The stability of a specific product is thus dependent, in a large measure, on its formulation, and its expiry date should be determined on the basis of stability studies carried out by the manufacturer. Studies undertaken with a view to determining the stability of a product under temperate conditions, however, do not necessarily provide a reliable indication of its shelf-life in tropical climates. In such cases, additional proof of stability should be requested from the manufacturer, who should assume responsibility for formulating a product that is stable under the climatic conditions prevailing in the countries of destination. Relevant information should be specifically requested by the national regulatory authority in the importing country within the context of the WHO Certification Scheme (see section 6 of this report). It is obviously impossible to obtain satisfactory assurances when a product is purchased through an intermediary if its provenance is unknown to the purchaser. For domestically produced products, the regulatory authority should evaluate stability data furnished by the manufacturer. The procurement agencies and the pharmacists responsible for drug distribution should ensure that they are supplied with adequate information concerning the proper storage and handling of each product.

Annex 1, on the stability of drug dosage forms, is a comprehensive statement on both the technical aspects of the subject and the responsibilities that devolve upon the manufacturer and all agencies and individuals responsible for the product throughout the distribution chain up to the time of its administration or delivery to the patient.

Within the distribution chain, the labelled expiry date on a pharmaceutical product has a dual significance: after this date, no formal assurance is provided regarding the condition of the product; and the manufacturer may no longer have legal liability for it. The Committee agreed that the use of time-expired stock should be entertained only in the most exceptional circumstances, when to withhold the stock would have serious consequences for patients. In every instance, the proposal to release such a product must be channelled through a pharmacist or other professional experienced in quality assurance and, when appropriate, referred to the
competent authority, which must decide on the necessity for analysis and the period of time during which the product may be used, having regard to all relevant circumstances. Doctors and other health professionals using the product may need to be alerted to the situation. Procurement procedures should be reviewed and, if necessary, modified to prevent such situations arising in the future.

The Committee recommends that:

1. The text of the requirements for Good Practices in the Manufacture and Quality Control of Drugs (1) should be revised to require that a precise expiry date be declared in uncoded form on the labelling of every pharmaceutical product.

2. WHO should develop guidelines on the stability data to be submitted in applications for product registration to national regulatory authorities.

3. Data and results of field studies on drug stability under extreme climatic conditions should be collected on a global scale.

4. WHO should promote research on the stability of certain multisource products containing substances on the WHO Model List of Essential Drugs and develop simple stability-indicating methods.

5. WHO should also request national authorities in countries with tropical or subtropical climates to identify products particularly vulnerable to degradation, as a basis for compiling a registry of products that require particular attention.

2. SAMPLING PROCEDURES

In Annex 1 of its thirtieth report the Committee presented guidelines on the management and operation of governmental drug control laboratories (“Good Laboratory Practices in Governmental Drug Control Laboratories”) (2). Many of the operations described there require the use of soundly based sampling procedures, and relevant guidelines for these are set out in Annex 2 to the present report.

Since analytical controls are frequently performed on only a small portion of the material under consideration, it is vital to ensure that the sample tested is reasonably representative of the whole.

The Committee emphasized that no single sampling plan is applicable to all situations. Different considerations and methodologies apply to in-process control, to batch release by
manufacturers, to routine control of consignments within the distribution chain, and to spot-sampling performed either by purchasers or by governmental inspectors.

The guidelines are intended primarily for use by national drug regulatory authorities and governmental procurement agencies, but the general principles and much of the advice are also applicable to manufacturers and wholesale dealers.

3. THE INTERNATIONAL PHARMACOPOEIA AND BASIC TESTS

3.1 Quality specifications for drug substances and dosage forms

The Committee noted that, with the publication of the third volume of the third edition of The International Pharmacopoeia in 1988 (3), monographs had been provided for almost all substances in the WHO Model List of Essential Drugs (4).

The Committee recommends the inclusion in The International Pharmacopoeia, firstly, of a series of general monographs for tablets, capsules and parenteral preparations and, secondly, of test methods for ascertaining uniformity of content and mass of single-dose preparations, for disintegration, and for sterility, supplemented by a general chapter on methods of sterilization. It recommends that these sections be issued as a separate fascicle, before their inclusion with other material in Volume 4, in order to ensure the wide availability of these important general texts at the earliest opportunity.

It noted that work was continuing on the development of additional general monographs, notably on dissolution tests, and that the feasibility of providing a method for control of particulate matter based on visual inspection was being explored. It further suggested that the Limulus amoebocyte lysate (LAL) test for bacterial endotoxins should also be considered for inclusion.

Guidance for those preparing or commenting on monographs for preparations to be included in The International Pharmacopoeia is attached as Annex 3.

3.2 Dissolution test for solid oral dosage forms

The dissolution rate is an important physical characteristic of a tablet, capsule or other solid oral dosage form. It
provides an estimate of the extent to which the drug substance is released from the dosage unit into a dissolution medium under standardized experimental conditions. It is thus a measure of the whole dissolution process and not just the initial degradation of the unit into granules or aggregates. It is generally accepted that, for certain drug substances, the disintegration test is not an adequate indicator of absorption in vivo and that a carefully designed dissolution test (which is now firmly established as a tool for batch-to-batch quality control) can be more predictive.

The Committee emphasized, none the less, that no in vitro test has yet been developed that offers a reliable means of assuring the therapeutic equivalence of chemically and pharmaceutically equivalent products. Dissolution requirements, when incorporated into The International Pharmacopoeia, must thus be regarded essentially as quality-control tools used to establish the release characteristics of specific solid oral dosage forms. Their adoption, however, could reasonably be expected to promote bioequivalence among multisource products. Having regard to expanding international trade in these products, the Committee considered it important that a dissolution test be developed for solid dosage forms within The International Pharmacopoeia as a matter of high priority. Because The International Pharmacopoeia is used primarily for governmental quality control in developing countries, it recognized that the selected test will be applied to preparations manufactured by a very large number of manufacturers operating nationally and internationally.

It recommends that, although the basket method is still used in some leading pharmacopoeias in the world, the “paddle” method be preferred because it is easily calibrated, simple and robust, and because the disintegration process can be monitored by direct observation. To foster harmonization of official requirements, it recommends that the specifications of the apparatus should comply with those already adopted by other pharmacopoeias, including The European Pharmacopoeia and The United States Pharmacopeia, but that the conditions under which tests are conducted—particularly with regard to the composition of the medium, the speed of rotation of the paddle, and the limits applied to them—should be adjusted to values established experimentally in internationally accredited developmental studies as providing the most consistent results for the specific substance in question.
It proposed that a dissolution test should be introduced only into monographs on preparations for which the disintegration test was not considered adequate for purposes of quality control, and it agreed that priority should be accorded, in the order shown, to the following short list of preparations drawn from WHO's Model List of Essential Drugs (4) that are widely considered to pose bioavailability problems:

- furosemide
- chloroquine
- ampicillin
- erythromycin
- isoniazid
- phenoxymethylpenicillin
- tetracycline
- griseofulvin
- digoxin
- levodopa
- metronidazole
- phenytoin
- mebendazole
- tolbutamide

In formulating these recommendations the Committee had regard to the results of a WHO-coordinated study involving governmental control laboratories in both developed and developing countries that had been conducted to assess interlaboratory variation in the results of dissolution tests performed on selected products widely available internationally.Remarkably consistent results had been obtained when the paddle apparatus was used. The Committee strongly recommends that the project be continued, that efforts be directed to increasing the number of participating laboratories, and that its scope be broadened to provide for comparisons of dissolution characteristics of locally available brands of multisource products. The Committee considered that the direct involvement of national laboratories in the further development of The International Pharmacopoeia, through collaborative projects of this nature, will not only promote the use of the Pharmacopoeia, but will also provide a direct and constructive way of ensuring adequate standards of analysis in the participating countries. In this connection the Committee wished to place on record its appreciation of the coordinating role and the considerable amount of developmental work undertaken by Professor J.-M. Aiache and his staff of the Biopharmacy Laboratory, Faculty of Pharmacy, University of Clermont-Ferrand, France.

Having regard to the need to establish biopharmaceutical parameters of new drug products while they remain under development, the Committee recommends that guidelines on the relevance of the dissolution test both during the various phases of
drug development and at the time of registration be prepared by WHO.

3.3 Microbiological contamination of nonsterile materials and products

The Committee acknowledged the need to ensure the absence of certain specified pathogens from raw materials of vegetable, animal and mineral origin (such as acacia, bentonite, gelatin, lactose, starch and tale). It also emphasized, however, the need to set appropriate limits for total microbial contamination of nonsterile dosage forms, at least in general guidelines that might be incorporated into a revision of the code of Good Practices in the Manufacture and Quality Control of Drugs (1).

3.4 Validation of analytical procedures

The Committee considered various proposals submitted by the Secretariat on the validation of analytical procedures used in the examination of pharmaceutical materials. It noted, however, that guidelines on this subject are also currently being developed by other pharmacopeial commissions and that further review and liaison are needed in this connection. It recommends that a small group of experts be convened to ensure the necessary collaboration.

3.5 Simple test methodology

The Committee expressed its appreciation of the considerable progress that continues to be made in the development of basic tests for confirming the identity of pharmaceutical substances and it commended the many laboratories and individuals who have contributed to this task. Tests for substances in some 150 different dosage forms are now in the final stages of preparation for publication by WHO.  

It noted that the Syndicat national de l'Industrie pharmaceutique, in France, is also developing some simplified quantitative analytical methods for assaying the content of pharmaceutical preparations.  

1 Basic tests for pharmaceutical dosage forms. Geneva, World Health Organization, in press.  
2 FABIATI, P. & PESEZ, M. Fiches d'identification et de dosage des médicaments; available in French from Syndicat national de l'Industrie pharmaceutique, 88 rue de la Faisanderie, 75116 Paris, France (English in preparation).
It agreed that, subject to validation of the methods in conformity with established working procedures, agreement should be sought to utilize this material, with due acknowledgement, in the further development of The International Pharmacopoeia.

4. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES AND INFRARED REFERENCE SPECTRA

4.1 Establishment of reference substances

Since the previous meeting of the Expert Committee, 12 new International Chemical Reference Substances had been established and replacement batches had been introduced for 5 previously established reference substances. The total collection now comprises 136 International Chemical Reference Substances and 13 Melting-Point Reference Substances (Annex 4). The Committee expressed its appreciation to the WHO Collaborating Centre for Chemical Reference Substances for the work accomplished and endorsed the Centre’s operational procedures.

The Committee was informed that since the previous meeting of the Committee the Centre had moved to new premises with considerably improved facilities and was again in a position to offer training to WHO fellows. It was emphasized that the operation of the Centre still resulted in considerable financial deficit, but that the National Corporation of Swedish Pharmacies had agreed to continue its support provided that further attempts be made to reduce the deficit. It was noted that WHO Headquarters had approached the WHO Regional Offices to seek financial support for reference substances distributed to government laboratories in the Member States of the various Regions and that, as a result, some alleviation of the financial burden now carried by the Centre might be expected. The Committee requested that its grateful acknowledgement be conveyed to the National Corporation of Swedish Pharmacies for its financial support of the WHO International Chemical Reference Substances programme. It also requested the Secretariat to continue its efforts to find means of supporting the Centre. It recognized that provision of the reference substances was a prerequisite for use of most of the specifications in The International Pharmacopoeia.
The Committee noted with satisfaction that the suggestion in the thirtieth report (2) that other laboratories experienced in the establishment of reference substances be invited to assist the Centre with laboratory examinations of candidate reference materials had been adopted on a trial basis, and that since the initial response had been promising, the approach was being further explored. In this connection, the valuable contribution of the National Biological Standards Laboratory, Canberra, Australia, was gratefully acknowledged.

The Committee also expressed great satisfaction that collaboration in the establishment of reference substances had been effected with several other pharmacopoeial organizations and it asked that due thanks be conveyed, in particular, to the European Pharmacopoeia Commission, the British Pharmacopoeia Commission, and the United States Pharmacopeial Convention Inc.

4.2 Validation of International Chemical Reference Substances

Having regard to the increasing collaborative involvement of national laboratories in the establishment of International Chemical Reference Substances, the Committee makes the following recommendations:

1. International Chemical Reference Substances should be established, as far as is possible, on the recommendation of the Committee. However, in order to expedite the establishment of urgently needed new reference substances and replacement batches, the WHO Collaborating Centre for Chemical Reference Substances should be authorized, after consulting with the WHO Secretariat, to proceed with the necessary analyses on its own initiative and with validation on the basis of advice from appropriately qualified experts.

2. International Chemical Reference Substances should be established primarily to support specifications adopted within The International Pharmacopoeia, but they may additionally be established for other purposes as deemed appropriate by the Committee. In every case, they should be certified for a defined use.

3. Ultimate responsibility for the adoption of the International Chemical Reference Substances should rest with the Committee.
It also recommends that the availability of new International Chemical Reference Substances be publicized in the periodical *WHO drug information.*

### 4.3 Infrared reference spectra

The Committee was informed that the project to develop methods of producing and validating reference spectra for verifying the identity of pharmaceutical substances by infrared spectrophotometry, as described in the thirtieth report of the Expert Committee (2, p. 16), was still in its pilot phase. To date, reference spectra for about 40 different substances had been prepared and circulated to collaborating laboratories for evaluation.

The Committee agreed that sufficient evidence had now been obtained to demonstrate the general feasibility of using reference spectra for this purpose. In a few instances, however, and notably in the case of polymorphic substances, reference spectra did not offer a satisfactory alternative to chemical reference substances. The Committee reaffirmed its opinion that reference spectra should not be produced for a substance if the corresponding monograph requires the use of a chemical reference substance for purposes other than identification.

The Committee noted that, whereas more than half the reference spectra produced to date were of the standard required for adoption, further expert advice was required regarding the means by which more suitable spectra of higher quality could be obtained for the remaining substances. It recommends that the procedures for validating these spectra should be analogous to those proposed by the Committee for International Chemical Reference Substances in section 4.2 above.

### 5. QUALITY ASSURANCE OF PRODUCTS MANUFACTURED BY RECOMBINANT DNA TECHNOLOGY

The Committee accepted that a need exists to develop international guidelines for assuring the quality of pharmaceutical preparations made by recombinant DNA technology. It recommends that proposals currently in draft form should be circulated to experts in both pharmaceutical and biological
standardization and it noted that a potential exists for collaboration between the two interested WHO Expert Committees—i.e., the present Committee and the WHO Expert Committee on Biological Standardization. Since it is already evident that chemical reference materials will be needed in the physicochemical control of at least some of these products, the Committee agreed that the establishment of such materials should be considered on a case-by-case basis.

In a preliminary review of the position the Committee noted, in particular, that:

(a) recombinant DNA technology is a rapidly evolving field and that a flexible approach to the control of these products is advisable to enable requirements to be modified in the light of accumulated experience of their production and use, and having regard to the continuing development of new technologies;

(b) while there is a need to provide generally applicable guidelines, individual products are likely to present specific quality control problems; methods of production and quality control of each product would therefore need to be given individual consideration, taking full account of any special features.

6. DEVELOPMENTS IN THE WHO CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE

The Committee noted that, by resolution WHA41.18, the Forty-first World Health Assembly had in 1988 adopted several substantive amendments to the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Annex 5). These bring within the ambit of the Scheme drug substances as well as finished dosage forms, and certain products intended for veterinary use as well as those for human use. They also require the competent authority in the exporting country to provide copies of all approved product information and labelling, as determined by the product licence.

The Committee was also informed that the need for sustained vigilance in the regulation and certification of pharmaceutical products had additionally been emphasized in another resolution (WHA41.16) which, inter alia, requests the Director-General "to initiate programmes for the prevention and detection of the export,
import and smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations” (5).

In reviewing various aspects of the implementation of the Scheme, the Committee emphasized that:

(a) Certification holds relevance to all finished pharmaceutical products, whether novel or long-established, whether marketed under generic or brand names, and regardless of the mechanism of ordering and purchase. If there is any doubt about the true origin of a product, the certification procedure loses its validity. Purchasers should be aware that some characteristics, e.g., stability and bioavailability of solid oral dosage forms, cannot be determined solely from analysis of the finished product, and, in the guidelines which the Secretariat is charged to develop, preparations featured in the WHO Model List of Essential Drugs that require particularly careful formulation to assure adequate quality in these particulars should be listed.

(b) Compliance with the provisions of the Scheme creates particular difficulties in the case of products bought by governments on open tender. It is most important, however, that the safeguards that it offers should not be lost in these circumstances. Procurement agencies are urged to indicate that only products that are duly certified in the country of origin will be considered in this context, and manufacturers who engage in tender business are advised to submit bids only for products that have already been certified by the competent national authority.

(c) As yet few national authorities are in a position to issue certificates for drug substances. This arises because full responsibility and liability for the quality of pharmaceutical products rest with the manufacturer of the finished dosage form, who is required to comply, in all aspects, with statutorily determined good manufacturing practices. These require, inter alia, rigorous control of all starting materials. Whereas several governments have recently introduced good manufacturing practices for starting materials, very few themselves undertake analyses of these substances. The Committee was informed that where this is done, a small but important number of consignments of imported substances needs to be rejected. It expressed concern that, in countries in which independent analytical control is not routinely required for these materials, the prevalence of substandard consignments may be significantly higher. It emphasized the need for
governments to ensure that effective quality control facilities, backed by statutory provisions, are in place wherever pharmaceutical production or drug formulation is undertaken.

(d) The Scheme requires oversight and implementation by appropriately qualified professionals, including experienced pharmacists, in both exporting and importing countries. Its provisions for the institution of inquiries if a product shows quality defects that are considered to be of a serious nature by the importing country and that are not attributable to local conditions and circumstances should always be observed. The strength of the Certification Scheme derives from the rigour with which it is implemented. Only if complaints are notified efficiently and investigated assiduously, can it be expected to achieve its full potential.

7. FALSELY LABELLED, SPURIOUS, COUNTERFEITED, AND SUBSTANDARD PHARMACEUTICAL PREPARATIONS

Serious concern is now expressed within some importing countries about the extent to which their standards of health care may be compromised by pharmaceutical products that, for various reasons, fall seriously short of pharmacopoeial requirements. The Forty-first World Health Assembly has requested the Director-General, within the context of the revised drug strategy (resolution WHA41.16), to initiate programmes for the prevention and detection of the export, import, and smuggling of such products (5).

At issue are products that are poorly formulated, degraded, or criminally inspired. The Committee emphasized that importing countries are rendered particularly vulnerable because the products that they receive have not always been subjected to the quality assessment and controls that are statutorily applied as a prerequisite to marketing in the country of origin. Indeed, it has been possible for unscrupulous individuals to set up companies engaged solely in exportation and to arrange their business in such a way as to escape all statutory controls in the countries from which they operate. In this case no check is made on whether they comply with prevailing standards of good manufacturing practices, or whether they actually
manufacture, or even handle at first hand, the products in which they trade.

Members were unanimous in their view that only adequate administrative preventive measures, in both exporting and importing countries, can ameliorate the situation. In importing countries the needs are fourfold:

(a) an effective national product-licensing system for pharmaceutical products must be established;
(b) the WHO Certification Scheme should be incorporated into national statutes or regulations;
(c) a small national drug quality-control laboratory, as described in an earlier report of the Committee (6), should be established;
(d) sampling of products within the distribution chain should be undertaken by governmental inspectors as an element in quality surveillance.

In this context, the Committee endorsed the report on guiding principles for small national drug regulatory authorities presented as Annex 6. It recognized the apparently daunting task that faces a small group of officials required to institute a formal system of product licensing and it emphasized, in particular, the need:

(a) for the development of standard computerized software packages to assist in this task;
(b) for WHO to sustain its efforts to exchange information on regulatory decisions of international relevance;
(c) for this information to be used as a resource in the routine operation of national licensing authorities.

8. TRAINING OF DRUG REGULATORS

In previous reports the Committee has provided general guidance relating to training in drug analysis. It wishes to emphasize the need to extend existing international efforts to ensure the training of responsible officers in all aspects of drug regulation and control. Annex 6 cogently depicts the degree of isolation in which many regulatory authorities are required to operate. Over the past decade, with the help of funds and collaboration from both government and nongovernmental organizations, including the Danish International Development Agency, the German Foundation for International Development, the International Federation of Pharmaceutical
Manufacturers Associations, and the World Federation of Proprietary Medicines Manufacturers, WHO has organized individual and group training for over 200 officials from drug regulatory authorities in developing countries. It is encouraging that funding agencies are now aware of the need for training in administrative and managerial aspects of drug regulation and control. Group training, allowing for free interchange of a variety of national experiences, is generally recognized to hold a considerable advantage over individual training in this connection. During the Fourth International Conference of Drug Regulatory Authorities, held in Tokyo in 1986, the WHO Secretariat was invited to collate the information on projected activities to ensure equitable distribution of efforts and resources.

The success of these training initiatives will depend, in large measure, on the availability of authoritative manuals and other teaching aids.

On WHO's invitation, the Industrial Pharmacists' Section of the International Federation of Pharmacists has produced a catalogue of training material in good manufacturing practice. Among related regional activities initiated within WHO, the Regional Office for the Americas has developed training modules, in Spanish, for good manufacturing practice and also for the management of drug quality-control laboratories.

REFERENCES


1 Catalogue of media for personnel training in good manufacturing practice (GMP) and related fields, *Manual for developing countries*: available in English from Pharmaceuticals, WHO, Geneva, Switzerland.
ACKNOWLEDGEMENTS

The Committee requested that its deep appreciation of the invaluable contributions to its work made over many years by the late Dr. C. A. Johnson be placed on record. Several of the background papers for its meeting had been prepared by him.

Acknowledgement is also made to Dr. S. Kopp-Kübel, Associate Professional Officer, WHO, who assisted in the preparation and proceedings of the meeting.

In addition to the expressions of appreciation contained within the body of its report, the Committee also acknowledges the valuable contribution to its work of the following institutions and persons:

WHO Collaborating Centre for Drug Quality Control, Pharmaceutical Branch, National Biological Standards Laboratory, Canberra, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China; WHO Collaborating Centre for Drug Information and Quality Assurance, National Institute of Pharmacy, Budapest, Hungary; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Central Drugs Laboratory, Government of India, Calcutta, India; WHO Collaborating Centre for Quality Assurance of Essential Drugs, National Quality Control Laboratory of Drug and Food, Directorate General of Drug and Food Control, Ministry of Health, Jakarta, Indonesia; WHO Collaborating Centre for Drug Management, Specialized Analytical Laboratory, University of Panama, Panama; WHO Collaborating Centre for Chemical Reference Substances, Central Laboratory, Apoteksbolaget AB, Stockholm, Sweden; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Drugs Analysis Division, Department of Medical Sciences, Ministry of Public Health, Bangkok, Thailand; WHO Collaborating Centre for Drug Quality Control, State Research Institute for the Standardization and Control of Drugs, Ministry of Health, Moscow, USSR.

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Annex 1

STABILITY OF DRUG DOSAGE FORMS

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1. INTRODUCTION

For industrially manufactured pharmaceutical products, especially those entering international commerce and/or distributed in territories with adverse climatic conditions, stability poses serious problems. Adequate stability may be achieved only through the combined efforts of all parties involved in product development, manufacture, registration, national quality surveillance, distribution, and use. It was pointed out at the Conference of Experts on the Rational Use of Drugs [Nairobi, 1985 (7)] that “no tests or certification schemes can prevent the gradual deterioration of products passing through a storage and distribution system and subjected to prolonged heat, humidity, rough handling and careless dispensing”.

The stability and expiry date of a product depend on its formulation and conclusions from stability studies carried out by the manufacturer during product development and cannot be assessed by simple analysis of the final product. Mandatory use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (2), which makes it possible to establish the true origin of the product and to distinguish between registered and unregistered products, can go a long way to providing
assurance of product stability. The reason for this is that registration of a dosage form in the exporting country means that the formulation has been examined by an independent government authority for its pharmaceutical characteristics, including stability, based on submission of results of stability studies carried out by the manufacturer and, where applicable, of bioavailability studies. It is acknowledged, however, that stability studies conducted for temperate climates may not be fully relevant to storage and distribution in countries with extreme climatic conditions and that additional proof of stability under extreme conditions may need to be requested from the manufacturers. In the absence of registration in the exporting country buyers have to rely solely on the firm's assurance and on their own professional knowledge to assess relevant stability data submitted by the firm. When the product is purchased from a broker, the manufacturer is often not known at all. In these cases, it is virtually impossible to obtain reliable information on product stability.

In 1979 the WHO Expert Committee on Specifications for Pharmaceutical Preparations, in the text on quality assurance in the pharmaceutical supply system annexed to its report, noted that an important facet of quality assurance concerns storage. It pointed out further that "inadequate ... storage can lead to physical deterioration and chemical decomposition, resulting in a reduction in activity ... as well as the formation of possibly harmful degradation products" (3). At a later date other aspects, such as microbiological instability and impaired bioavailability, started to be considered.

The importance of factors related to storage, such as expiry dating (shelf-life), has been recognized. The Twenty-fifth World Health Assembly requested the Director-General in 1972 to undertake a study of the most feasible means of indicating, by a uniform system of marking, the limits of shelf-life of pharmaceutical products under the recommended conditions of their storage, as well as the date of manufacture and batch number (resolution WHA25.61).

In the past WHO has addressed some of the issues related to drug stability and storage. Recommendations have been formulated on the inclusion of the batch number, expiry date and date of manufacture in the text of drug labels (3–5). Results of accelerated stability studies and a manual for simplified tests permitting the detection of gross degradation of the least stable substances have been published (6).
The Organization is often asked for information and advice with regard to stability of finished pharmaceutical products. Particular interest in the issue of drug stability was expressed by many delegates at the Forty-first World Health Assembly, in 1988, during the discussion on the implementation of the revised drug strategy. The present document is an attempt to summarize basic principles in this area. It is addressed to policy-makers, health ministries, manufacturers, procurement agencies, and workers in the distribution system. It may be supplemented in future by technical advice in specific areas.

The document is concerned with industrially manufactured dosage forms and not with those prepared in the pharmacy or reconstituted in the hospital. Although many points discussed apply also to preparations of biological origin and radiopharmaceuticals, this document is not primarily intended for that purpose. The use of terms that occur most frequently in discussing these issues is explained in section 4.

2. GENERAL CONSIDERATIONS

The most important factors that may influence the degree and rate of deterioration of drug products are the following:

(a) Environmental factors such as heat, moisture, light, oxygen and various other forms of physical stress and changes (for example, vibration or freezing).

(b) Product-related factors. These may include:

(i) the chemical and physical properties of the active drug substance and of the pharmaceutical aids (excipients) used (for example, the presence of certain impurities, the particular polymorphic or crystal form, the particle size and the possible presence of water or other solvents);

(ii) the dosage form and its composition;

(iii) the manufacturing process used (including environmental conditions and technological procedures);

(iv) the nature of the container or other packaging with which the product may be in direct contact or which may otherwise influence the stability.

All the above factors have to be considered when establishing the shelf-life of a product.
The stability of the finished product depends to a large degree upon the stability of the drug substance it contains. At the same time it should be noted that formulation and packaging may exert a positive or a negative influence on the stability of the active substance.\textsuperscript{1} In section 5 drug substances are listed that were found to be less stable under simulated tropical conditions. All other factors being equal, finished products containing these substances require particular attention from the stability viewpoint.

For each product the shelf-life has to be established on the basis of stability testing. For practical reasons of commerce and distribution, a stated shelf-life exceeding five years is not recommended. Shorter shelf-lives may be expected for numerous active ingredients, e.g., antibiotics and vitamins, or for some types of dosage form, e.g., certain aqueous solutions, emulsions or creams. Products developed and packaged for a temperate climate may not necessarily be suitable for distribution in tropical zones.

The stability overage\textsuperscript{2} is acceptable only in limited cases and on grounds of scientific and practical justification.

The use of time-expired drugs should be strongly discouraged. Only in exceptional cases, e.g., emergencies, should the use of such products be considered. The decision to utilize such products may be taken on a case-by-case basis by a responsible national health authority only, and then after careful weighing of all relevant factors by a competent professional. In such cases, samples of these products have to be retested against pharmacopoeial or similar standards by stability-indicating methods such as chromatography, attention also being paid to microbiological aspects. The economic loss and health hazards arising from the rejection of expired stock should be balanced against risks of impaired efficacy and safety. The availability of other appropriate medicines and, or the practicability of replenishing stocks should be taken into consideration. The eventual liability problems should be considered since the expiry date indicates the moment at which the manufacturer's liability for the product may be relinquished. Whenever feasible, such a decision should be taken after consultation with the manufacturer as well as with independent experts. When a decision is taken to use time-

\textsuperscript{1} It follows that the stability of a product is producer-specific.

\textsuperscript{2} An excess of the active drug substance in a dosage form, added at the time of manufacture to compensate for the expected loss of potency during storage.
expired material, a new expiry date, well defined and as limited as practicable, has to be established.

3. RESPONSIBILITY OF PARTIES INVOLVED IN THE ASSURANCE OF DRUG STABILITY

3.1 Manufacturers

As stated in Good Practices in the Manufacture and Quality Control of Drugs (4), it is the responsibility of manufacturers to ensure the quality of the drugs they produce. Similarly, they have the responsibility to develop appropriate dosage forms (including packaging) that are adequately stable under climatic conditions prevailing in the country or countries in which the preparations are intended to be used.

The manufacturer must establish the shelf-life of the product in relation to recommended storage conditions by using an appropriate stability-testing programme. Full details of the work carried out to establish the shelf-life should be made available to drug regulatory authorities. The expiry date and recommended storage conditions must be communicated to all involved in the pharmaceutical supply system and to patients; it is recommended that this information should be given on the label. When necessary, the utilization period must be determined and additionally specified on the label.

3.2 Drug regulatory authorities

Drug regulatory authorities must request adequate stability data from manufacturers in support of their claims concerning the shelf-life of registered products relevant to their countries. These data must be evaluated in the light of scientific knowledge and experience.

They should develop means to ensure that relevant information on shelf-life and storage conditions is readily available to all concerned, for example by establishing regulations on labelling. They should ensure, when inspections of manufacturing establishments are carried out in accordance with the requirements of Good Practices in the Manufacture and Quality Control of Drugs (4), that appropriate stability-testing programmes for marketed products are being followed.

Guidelines and inspections are necessary to ensure that drug products are adequately handled and stored in the pharmaceutical
supply system—for example, by requiring that the temperature regimen recommended by the manufacturer is followed, that there is appropriate control of other environmental factors, that a proper system of stock rotation ("first-in-first-out" rule) is maintained, and that expired products are destroyed. More detailed consideration of such factors is to be found in publications by FIP and IFPMA (7) and others (8, 9). The importance of adequate storage facilities cannot be overemphasized. Experience in many countries proves that investment in warehouses is cost-effective. Products should be monitored by random visual inspection and where possible by laboratory testing at various stages in the distribution system (including hospital wards).

3.3 Procurement agencies

Procurement agencies should require sufficient information on the composition, the process of manufacture, stability, and provisions for appropriate labelling to be included in the drug procurement documents. Where possible, this information should be checked against data provided for registration purposes. In cases where the date of manufacture is not indicated on the label of a product, this information should be given in the accompanying documentation. In addition, the procurement agencies should inform potential suppliers of any extreme environmental conditions that might prevail.

3.4 Pharmacists and other workers in the supply system

Normally the supply system should be under the direct control of a pharmacist. When this is not possible, the responsible person should be under pharmaceutical supervision and have adequate training.

The responsible person should ensure that:

(a) Older stock is dispensed first and attention is paid to the expiry dates.

(b) Products are stored according to the recommended storage conditions, as stated on the label, etc.

(c) Products are observed for evidence of instability.\(^1\)

\(^1\) General requirements for drug dosage forms will be published in *The International Pharmacopoeia.*
(d) Products that are repackaged or further processed are properly handled and labelled.

(e) Products are dispensed in the proper containers with the proper closures.

(f) Patients are educated and informed concerning the proper storage and use of the products, including the disposal of outdated or excessively aged prescriptions.

4. USE OF TERMS

The following working definitions or explanations are offered for a number of the terms used in this text.

**Stability:** The ability of a drug to retain its properties within specified limits throughout its shelf-life. The following aspects of stability are to be considered: chemical, physical, microbiological and biopharmaceutical.

**Expiry (expiration) date:** The expiry date placed on the container of a drug product designates the date up to and including which the product is expected to remain within specification if stored correctly. It is established for every batch by adding the shelf-life period to the manufacturing date.

**Shelf-life (expiration dating period or validity period):** The period of time during which a drug product is expected, if stored correctly, to remain within specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

**Provisional (tentative) shelf-life:** The provisional shelf-life is determined by projecting results from accelerated stability studies.

**Date of manufacture:** A date fixed for the individual batch, indicating the completion date of the manufacture. It is normally expressed by a month and a year. The date of the release analysis may be taken as a date of manufacture, provided that the period between the beginning of production and the release of the product is not longer than one-twentieth of the shelf-life.

**Normal storage conditions:** Storage in dry, well-ventilated premises at temperatures of 15–25°C or, depending on climatic
conditions, up to 30 °C. Extrinsic odours, other indications of contamination, and intense light have to be excluded.

**Defined storage instructions:** Drug products that must be stored under defined conditions require appropriate storage instructions.

Unless otherwise specifically stated, e.g., continuous maintenance of cold storage, deviation may be tolerated only during short-term interruptions, for example during local transportation.

The following instructions are recommended:

<table>
<thead>
<tr>
<th>On the label</th>
<th>Means:</th>
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<tbody>
<tr>
<td>&quot;Do not store over 30 °C&quot;</td>
<td>from + 2 °C to + 30 °C</td>
</tr>
<tr>
<td>&quot;Do not store over 25 °C&quot;</td>
<td>from + 2 °C to + 25 °C</td>
</tr>
<tr>
<td>&quot;Do not store over 15 °C&quot;</td>
<td>from + 2 °C to + 15 °C</td>
</tr>
<tr>
<td>&quot;Do not store over 8 °C&quot;</td>
<td>from + 2 °C to + 8 °C</td>
</tr>
<tr>
<td>&quot;Do not store below 8 °C&quot;</td>
<td>from + 8 °C to + 25 °C</td>
</tr>
</tbody>
</table>

"Protect from moisture" no more than 60% relative humidity in normal storage conditions; to be provided to the patient in a moisture-resistant container.

"Protect from light" to be provided to the patient in a light-resistant container.

**Stability tests:** The purpose of stability tests is to obtain information in order to define the shelf-life of the pharmaceutical product in its original container and to specify storage conditions.

**Accelerated (stress) stability studies:** Studies designed to increase the rate of chemical or physical degradation of a drug by using exaggerated storage conditions with the purpose of monitoring degradation reactions and predicting the shelf-life under normal storage conditions. The design of accelerated studies may include elevated temperature (e.g., 37–40 °C and up to 50–55 °C), high humidity and light.

Only a provisional shelf-life may be established on the basis of these studies. Therefore, accelerated studies should always be supplemented by real-time studies under expected storage conditions.

**Utilization period:** A period of time during which a reconstituted preparation or the preparation in an opened multidose container can be used.
5. LESS STABLE DRUG SUBSTANCES

The experimental conditions used to compile this list of less stable substances were the following: initial exposure for 30 days to air at 50 °C and 100% humidity; if no degradation was demonstrable after this time, the temperature was raised to 70 °C for a further period of 3–7 days. All other factors being equal, finished products containing the following substances require particular attention from the stability viewpoint.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Substance</th>
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<tbody>
<tr>
<td>acetylsalicylic acid</td>
<td>ephedrine sulfate</td>
</tr>
<tr>
<td>aminophylline</td>
<td>epinephrine</td>
</tr>
<tr>
<td>amitriptyline hydrochloride</td>
<td>epinephrine hydrogen tartrate</td>
</tr>
<tr>
<td>ammonium chloride</td>
<td>ergocalciferol</td>
</tr>
<tr>
<td>amphotericin B</td>
<td>ergometrine hydrogen maleate</td>
</tr>
<tr>
<td>ampicillin sodium</td>
<td>ergotamine maleate</td>
</tr>
<tr>
<td>ampicillin trihydrate</td>
<td>ergotamine tartrate</td>
</tr>
<tr>
<td>antimony sodium tartrate</td>
<td>ethosuximide</td>
</tr>
<tr>
<td>ascorbic acid</td>
<td>ethylmorphine hydrochloride</td>
</tr>
<tr>
<td>bacitracin</td>
<td>ferrous sulfate</td>
</tr>
<tr>
<td>bacitracin zinc</td>
<td>fluphenazine decanoate</td>
</tr>
<tr>
<td>benzathine benzylpenicillin</td>
<td>fluphenazine hydrochloride</td>
</tr>
<tr>
<td>benzylpenicillin potassium</td>
<td>formaldehyde solution</td>
</tr>
<tr>
<td>benzylpenicillin sodium</td>
<td>genticin sulfate</td>
</tr>
<tr>
<td>bephenium hydroxynaphthoate</td>
<td>guanethidine sulfate</td>
</tr>
<tr>
<td>calcium gluconate</td>
<td>hexylresorcinol</td>
</tr>
<tr>
<td>calcium para-aminosalicylate</td>
<td>hydralazine hydrochloride</td>
</tr>
<tr>
<td>carbenicillin sodium</td>
<td>hydrocortisone sodium succinate</td>
</tr>
<tr>
<td>cefalexin</td>
<td>hydroxocobalamin</td>
</tr>
<tr>
<td>chloral hydrate</td>
<td>hyoscyamine sulfate</td>
</tr>
<tr>
<td>chloramphenicol sodium succinate</td>
<td>imipramine hydrochloride</td>
</tr>
<tr>
<td>chlorphenamine hydrogen maleate</td>
<td>ipecacuanha powder</td>
</tr>
<tr>
<td>chlorpromazine hydrochloride</td>
<td>isoprenaline hydrochloride</td>
</tr>
<tr>
<td>chlortetracycline hydrochloride</td>
<td>isoprenaline sulfate</td>
</tr>
<tr>
<td>cloxacillin sodium (monohydrate)</td>
<td>lidocaine hydrochloride</td>
</tr>
<tr>
<td>codeine phosphate</td>
<td>melarsoprol</td>
</tr>
<tr>
<td>colecalciferol</td>
<td>mercuric oxide yellow</td>
</tr>
<tr>
<td>dalpensone</td>
<td>metrifonate</td>
</tr>
<tr>
<td>dexamethasone sodium phosphate</td>
<td>naloxone hydrochloride</td>
</tr>
<tr>
<td>dicloxacillin sodium (monohydrate)</td>
<td>neomycin sulfate</td>
</tr>
<tr>
<td>diethylcarbamazine dihydrogen citrate</td>
<td>nystatin</td>
</tr>
<tr>
<td>doxycycline hyclate</td>
<td></td>
</tr>
<tr>
<td>emetine hydrochloride</td>
<td></td>
</tr>
<tr>
<td>ephedrine</td>
<td></td>
</tr>
</tbody>
</table>

32
orciprenaline sulfate  
salbutamol sulfate
oxytetracycline hydrochloride  

paromomycin sulfate  
senna leaf
penicillamine  
silver nitrate
phenobarbital sodium  
sodium calcium edetate
phenoxymethylpenicillin  
sodium lactate
phenoxymethylpenicillin calcium  
sodium nitrite
phenoxymethylpenicillin potassium  
sodium para-aminosalicylate
phenolamine mesilate  
sodium stibogluconate
phenylbutazone  
sulfacetamide sodium
pilocarpine hydrochloride  
sulfadiazine sodium
pilocarpine nitrate  
sulfadimidine sodium
procainamide hydrochloride  
suxamethonium chloride
procaine benzylpenicillin  
tetracaine hydrochloride
procaine hydrochloride  
tetracycline hydrochloride
procarbazine hydrochloride  
thiamine hydrochloride
promazine hydrochloride  
thiamine mononitrate
promethazine hydrochloride  
thiopental sodium
pyridoxine hydrochloride  
tolbutamide
quinine bisulfate  
undecylenic acid
quinine dihydrochloride  

REFERENCES

# Annex 2

## SAMPLING PROCEDURE FOR INDUSTRIALLY MANUFACTURED PHARMACEUTICALS

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</tr>
</tbody>
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## 1. GENERAL CONSIDERATIONS

Sampling comprises the operations designed to select a portion of a pharmaceutical material for a defined purpose. The sampling procedure must be adapted to the purpose of sampling, to the type of controls intended to be applied to the samples, and to the material to be sampled. The procedure should be described in a written protocol.

### 1.1 Purpose of sampling

Sampling may be required for different purposes such as: acceptance of consignments; clearance of batches; in-process
controls; special controls; inspection for customs clearance, deterioration, adulteration, etc.; or obtaining a retention sample.

1.2 Types of controls

The controls intended to be applied to the sample may be:

(a) checking the identity of a material;
(b) performing complete pharmacopoeial or analogous testing; or
(c) performing special tests.

1.3 Classes and types of materials

The materials to be sampled may belong to the following classes:

(a) Bulk materials, represented by:
   (i) starting materials (including both drug substances and pharmaceutical aids) in solid, liquid, or semi-solid state;
   (ii) vegetable drugs, such as leaves, herbs, flowers, seeds, fruits, roots, rhizomes and bark, in whole or broken state.

Special care may be needed for certain bulk materials, for example, for those that are very potent, toxic, hygroscopic, or light-sensitive, or require special microbiological precautions.

(b) Intermediates in the manufacturing process.

(c) Drug products (in-process as well as before and after packaging). For finished drug products the sampling procedure must take account of the official and nonofficial tests required for the individual dosage form (for example, tablets, parenteral preparations).

(d) Containers, packaging materials, and labels.

The sampling procedure must take account of the homogeneity and uniformity of the material.

(a) Homogeneity. A material is regarded as homogeneous when it is all of the same origin (for example, from the same batch) and as nonhomogeneous when it is of differing origins.

(b) Uniformity. A starting material may be considered uniform when samples drawn from different layers do not show significant differences in the quality-control tests. The following materials may be considered uniform unless there are signs to the contrary: organic and inorganic chemicals, purified natural products, various processed natural products like fatty oils and essential oils, plant
extracts. The assumption of uniformity is strengthened by homogeneity, i.e., when the consignment is derived from a single batch.

Signs of nonuniformity include differences in shape, size or colour of particles in crystalline, granular or powdered solid substances, moist crusts on hygroscopic substances, deposits of solid material in liquid or semi-liquid products, and stratification of liquid products. Such changes, some of which may be readily reversible, can occur during prolonged storage or exposure to extreme temperatures during transportation.

Dosage forms may be considered uniform when different samples from the same batch comply with the relevant tests for uniformity.

Finally the sampling procedure must take account of the past experience with the material and with the supplier, and of the number of sampling units in the consignment.

1.4 Parties concerned with sampling procedures

Parties concerned with sampling procedures include:

(a) manufacturers, in the context of good manufacturing practice (GMP);
(b) customers, such as governmental or nongovernmental agencies involved in the acquisition of drug products;
(c) drug control authorities, responsible for the clearance of drug products held in quarantine after manufacture or importation, and for the detection of materials that have deteriorated or have been contaminated or adulterated.

These guidelines are intended primarily for drug control authorities and governmental procurement agencies, but the general principles may also be appropriate for the other parties referred to above.

2. USE OF TERMS

The following working definitions or explanations are offered for a number of the terms used in this text.
2.1 Sampling operations

Sampling procedure: The complete sampling operations to be applied to a defined material for a specific purpose. A detailed written description of the sampling procedure is provided as the sampling protocol.

Sampling method: Section of the sampling procedure dealing with the method prescribed for withdrawing samples.

Sampling plan: Description of the number of units or quantity of material that must be collected.

Sampling record: Written record of the sampling operations carried out on a particular material for a defined purpose. The sampling record must contain the date and place of sampling, a reference to the sampling protocol used, a description of the containers and of the materials sampled, notes on possible abnormalities, together with any other relevant observations and the name and signature of the inspector.

2.2 Samples

Sample: A portion of a material collected according to a defined sampling procedure. The size of any sample should be sufficient to carry out all anticipated test procedures, including all repetitions. If the quantity of material available is not sufficient for the intended analyses and for the retention samples, the inspector must record that the sampled material is the available sample (see below) and the evaluation of the results must take account of the limitations deriving from the insufficient sample size.

Samples should be stored in accordance with storage instructions for the respective drug; closures and labels should be of such a kind that unauthorized opening can be detected.

Available sample: Whatever total quantity of sample material is available.

Final sample: Sample ready for the application of the test procedure.

Original sample: Sample collected directly from the material.
**Pooled sample:** Sample resulting from the pooling of all or parts of two or more samples of the material.

**Random sample:** Sample in which the different fractions of the material have equal probability of being represented.

**Representative sample:** Sample obtained according to a sampling procedure designed to ensure that the different properties of a nonuniform material are proportionately represented.

**Retention sample:** Sample collected and reserved for future controls. The size of a retention sample should be sufficient to allow at least two confirmatory analyses. In some cases statutory regulations may require one or more retention samples, each of which must be separately packaged and sealed.

**Selected sample:** Sample obtained according to a sampling procedure designed to select a fraction of the material that is likely to have special properties. A selected sample that is likely to contain deteriorated, contaminated, adulterated or otherwise unacceptable material is known as an **extreme sample**.

### 2.3 Quantities of material

**Batch:** "A quantity of any drug produced during a given cycle of manufacture." If the manufacturing process is continuous, the batch originates in a defined period of time during which the manufacturing conditions have not been modified.

**Consignment:** Quantity of a bulk starting material, or of a drug product, made by one manufacturer that is supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

**Sampling unit:** Discrete part of a consignment, such as an individual package, drum or container.

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1 As defined in *Good Practices in the Manufacture and Quality Control of Drugs (WHO Official Records, No. 226, 1975, p. 88).*

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2.4 Personnel

*Sampling inspector:* Person responsible for performing the sampling operations. The sampling inspector need not be a qualified analyst. However, everyone called upon to take samples should be trained in the practical aspects of sampling and should have sufficient knowledge of pharmaceutical substances to execute the work effectively and safely. A conscientious approach, with meticulous attention to detail and cleanliness, is essential. The sampling inspector must remain alert to any signs of contamination, deterioration or tampering. Any suspicious signs should be recorded in detail in the sampling record.

3. GENERAL PRECAUTIONS TO BE TAKEN DURING SAMPLING OPERATIONS

All operations related to sampling should be performed with care, using proper equipment and tools. Any contamination of the sample by dust or other foreign material is liable to jeopardize the validity of the subsequent analyses.

For the sampling of products at warehouses, the responsible person should have at his or her disposal all the tools needed to open the packages, barrels, containers, etc., including knives, pliers, saws, hammers, wrenches, implements to remove dust (such as brushes), and material to reclose the packages (such as sealing tape), as well as self-adhesive labels to indicate that a part of the contents has been removed from a package or container.

Sampling of uniform starting materials does not require complicated tools. A variety of pipettes fitted with suction bulbs, cups or beakers, dippers, and funnels are needed for liquids of low viscosity. A glass rod can be used for highly viscous liquids; and spatulas or scoops are needed for powdered and granular solids. A porcelain or stainless steel spoon which can be sterilized by heating is suitable for sampling sterile powders.

Tools for sampling nonuniform materials are more complicated and more difficult to clean. A sampling tube with a shutter at the lower end is used to sample liquids in drums or other large containers. The tube is inserted vertically to the full depth of the drum, the lower end is then closed and the core removed. To sample solids, a slotted tube with a pointed end is used. It is inserted horizontally with the slot downmost and then turned through 180°.
When withdrawn, it captures material along its entire length. A double-tubed trier may also be used to remove a portion from the whole length of a large container. Before being sampled, lumped solids must be ground to powder in a mortar.

All tools and implements should be kept scrupulously clean. Before re-use they should be thoroughly washed, rinsed with water or a suitable solvent, and dried. Adequate washing facilities should be provided in warehouses, otherwise inspectors will need to bring separate clean sets of sampling implements for each product.

Sampling from large containers of starting material or bulk products can present difficulties. Whenever possible, this work should be carried out in a separate closed cubicle within the warehouse in order to reduce the risk of contamination by dust of either the sample or the remaining material in the container, or cross-contaminations. For sterile materials, sampling should be carried out under aseptic conditions.

Sampling of drug products in retail containers from outlets such as pharmacies or hospitals in general does not present problems, save that the inspector should ensure that the material taken is sufficient for the intended analyses and for the retention samples, and that all sampling units are derived from the same batch.

4. PACKAGING AND LABELLING OF SAMPLES

The container used to store a sample should not interact with the sampled material nor allow contamination. It should also protect the sample from light, air, moisture, etc., as required by the storage directions for the material sampled. As a general rule, the container should be sealed and tamperproof. The container must be properly labelled.

Samples of loose materials, whether solid or liquid, should be placed in one or more clean containers. Liquid samples should be transported in glass bottles closed by screw-tops with inert liners that provide a good vapour-proof (moisture-proof) seal for the contents. Glass screw-top jars are preferable also for solid or semi-solid materials, but metal tins may be used when there is no risk of chemical interaction. In this case the lids should be taped shut. The use of plastic containers is not recommended. Light-sensitive materials should be protected by using amber glass containers or by wrapping colourless glass containers in black paper.
Solid dosage forms, such as tablets or granules, should be protected during transit, either by totally filling the container with the product or by filling any residual space with a suitable material. All containers should be sealed and labelled and all samples from an individual sampling unit of a single consignment should be transported in a single sealed box that is adequately packaged to avoid breakage in transport.

All containers that come apart (e.g., screw-capped jars, metal tins with separate lids) should be labelled on all parts to avoid cross-contamination when they are opened for examination.

If one sample is divided into several sample containers, they should be transported in a single, sealed box, labelled to identify the product, the consignment from which the sample was drawn, the size of the sample, the date and the place of sampling, and the name of the inspector. If the sample is collected in one container only, which is already provided with a tamperproof seal, the label with the necessary information may be attached directly to the container.

Security and adequate storage conditions must be ensured for the rooms where samples are stored.

Supervision of the sampling process should also be provided.

5. SAMPLING DURING PHARMACEUTICAL INSPECTIONS

Pharmaceutical inspectors may be called upon to take samples from retail or hospital pharmacies or from industry and wholesalers, either on a routine basis or in a variety of special circumstances, such as:

— following the discovery of products that show signs of possible deterioration, contamination or adulteration;
— when a particular product is suspected of being either ineffective or responsible for adverse clinical reactions;
— when preparations are compounded on the premises.¹

For deteriorated dosage forms, the sample should consist of one or several retail containers of the product that shows visual signs of deterioration.

¹ For an individually compounded medicine prepared on a physician's prescription, the whole container with its contents is usually taken.
When a complaint has been received about a drug product, the sample should include the original container and, if possible, one or more containers with their content of the same product bearing the same batch number.

6. SAMPLING OF PHARMACEUTICAL DOSAGE FORMS IN REGULAR SURVEILLANCE PROGRAMMES ON DRUG QUALITY DURING MARKETING

National drug control authorities hold the responsibility to monitor the quality of all drug products marketed in the territory of their competence. The extent to which routine surveillance, as opposed to assessment of suspect products, should be undertaken will depend upon the capacity of the national quality-control laboratory, the extent to which the quality of products is assessed prior to registration, the extent to which the requirements for good manufacturing practice are implemented, and the number of products that are imported from abroad.

A systematic programme of drug quality surveillance should aim at regular sampling of all marketed products whether registered for sale or compounded in pharmacies. Each product should be assessed at least once every two to three years, but particular attention should be accorded to products that are of prime importance to public health programmes or that are potentially dangerous, unstable, or difficult to formulate properly.

The programme of sampling should be drawn up by the responsible laboratory, if necessary under the guidance of the drug control authority, on a yearly or half-yearly basis. This programme should not only list the products to be sampled during a given period, but should also specify the sampling procedures and the size of the samples to be collected, taking into account the need for retention samples. The programme should determine to what extent each brand of a given product will be sampled and which local authority or inspector will be responsible for each sampling operation, and it should indicate to which laboratory (if more than one exists) each sample should be sent. Such a programme enables the facilities of each laboratory to be used to best advantage.
7. SAMPLING OF PHARMACEUTICAL DOSAGE FORMS FOR ACCEPTANCE OF CONSIGNMENTS

The quality of consignments of finished pharmaceutical products frequently needs to be verified at the time of their importation or purchase. The necessary sampling should be performed in accordance both with an appropriate method and with regard to the presumed homogeneity or nonhomogeneity and uniformity or nonuniformity of the consignments. Thus, a consignment of a product from a single manufacturer labelled with a single batch number is assumed to be homogeneous. This assumption is further strengthened in the case of imported products provided with a batch certificate issued in the country of origin in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.¹

If these conditions apply and if the size of the batch is reasonable, a single sample for the intended analyses and a single retention sample will suffice. The size of the samples will be determined by the requirements of the analytical procedure according to which the product will be tested. Tests of unit dosage forms for uniformity of weight, volume or content can require a considerable number of units as can tests for sterility. Depending upon the type of the material, the size of the consignment, and the way in which the material is packaged, a sampling unit may be regarded as a box of vials or a box of jars of tablets rather than one of the individual vials or jars. The required number of unit dosage forms is then withdrawn from any individual container in the selected box.

If the consignment consists of one very large batch, or if little experience has been obtained with the product to be sampled, it may be prudent to carry out two independent analyses. Two independent final samples must then be taken from different sampling units. Conversely, when a consignment of moderate size is composed of two or three batches from the same manufacturer, a single sample may suffice, provided that favourable experience has previously been gained with the product and that there is evidence from the expiry date or other information that the batches were produced at approximately the same time.

Pharmaceutical forms supplied in bulk may also need to be examined. These include liquids and semi-solid materials, powdered solids or granulates transported in large containers and intended either for further processing or for direct packaging into final market containers, and unit dosage forms (tablets, capsules) supplied in bulk intended for repackaging into smaller containers.

Unless there is evidence to the contrary, products of this kind labelled with the name of the manufacturer and a single batch number may be assumed to be uniform if they have been produced in accordance with good manufacturing practice and are provided with a certificate issued in the country of origin according to the WHO Certification Scheme. In these circumstances the collection of a single sample sufficient for the intended analyses is adequate.

8. SAMPLING OF STARTING MATERIALS

8.1 General considerations

Drug control laboratories are less frequently involved in the sampling of pharmaceutical starting materials, although they may be called upon to assess the quality of imported consignments. Again, this assessment must be undertaken using samples collected in accordance with an appropriate procedure, because a poorly collected sample may provide misleading information. The sampling procedure must have regard to whether or not the material can reasonably be considered as uniform. A more complex procedure must be employed when there is a suspicion of nonuniformity.

If the material of a consignment can be regarded as uniform, the sample can be taken from any part of the consignment. If, however, the material is not physically uniform, special sampling tools may be required to withdraw a cross-sectional portion of the material. In some instances, however, an attempt can be made to restore the uniformity of the material before sampling. Thus, a stratified liquid may be stirred, or a solid deposit in a liquid may be dissolved by gentle warming and stirring. Such interventions are difficult when the containers are large and they should not be attempted without adequate knowledge of the properties of the contents.

All partially processed natural products, both herbal (dried plants and their parts) and mineral, should be treated as intrinsically nonuniform. Special procedures requiring considerable practice are
used to prepare representative samples from such consignments, including coning and quartering and the treatment of fines. These procedures are not further described in these guidelines.¹

8.2 Sampling plans for consignments of starting materials supplied in several sampling units

As already stated, these guidelines are intended primarily for drug control authorities and governmental agencies and are not necessarily appropriate for other parties such as experienced manufacturers with established and time-tested sampling procedures. Manufacturers with limited experience may wish to follow some of these recommendations.

Ideally, each sampling unit should be examined in order to check for intactness or possible damage of the container, and the content should be inspected for uniformity and chemically tested for identity. Uniformity should be tested on selected layer samples at different points of the material without previous intermixing. However, this ideal procedure is not always possible or justified by the purpose of sampling; a number of sampling units should then be randomly selected for sampling. Also it is not prudent to open all containers of products liable to deteriorate under the influence of moisture or oxygen when these are held in a transit warehouse. However, materials in damaged containers or found to be nonuniform must either be rejected or individually sampled for a complete quality control. Unlabelled sampling units must be rejected.

For random sampling, whenever possible each sampling unit is consecutively numbered and the required number of sampling units is then selected at random using tables of random numbers. The number of units depends on different assumptions and three plans in this regard are given below.

Control laboratories of manufacturers are required to analyse and release or reject each received consignment of the starting materials used to produce a drug product. For this purpose they

need samples of each sampling unit of a drug substance or a pharmaceutical aid in order to be able to check the identity of the material. These samples subsequently may be pooled in one way or another to perform a full analysis. While for drug substances such a procedure should always be followed, it may be considered not practical or unnecessary for selected pharmaceutical aids.

8.2.1 The “n plan”

The “n plan” should be used with great caution and then only when the material is considered uniform and is supplied from a well-known source. The samples can be withdrawn from any part of the container (usually from the top layer). The “n plan” is based on the formula \( n = \sqrt{N} \), where \( N \) is the number of sampling units in the consignment. The value of \( n \) is rounded up to the next higher integer. According to this plan, original samples are taken from \( n \) sampling units selected at random and these are subsequently placed in separate sample containers. The control laboratory inspects the appearance of the material and tests the identity of each original sample according to the relevant specification; if the results are concordant, the original samples are pooled into a final sample from which an analytical sample is prepared, the remaining part being kept as a retention sample. The “n plan” is not recommended for use by control laboratories of manufacturers who are required to analyse and release or reject each received consignment of the starting materials used to produce a drug product.

8.2.2 The “p plan”

The “p plan” may be used when the material is uniform and is received from a source that is well known and when the main purpose is to check the identity. The “p plan” is based on the formula \( p = 0.4 \sqrt{N} \), where \( N \) is the number of sampling units. According to this plan, samples are taken from each of the \( N \) sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory, visually inspected and tested for identity (simplified methods may be used), and, if the results are concordant, \( p \) final samples are formed by appropriate pooling of the original samples.
8.2.3 *The "r plan"

The "r plan" may be used when the material is suspected to be nonuniform and/or is received from a source that is not well known. The "r plan" may also be used for vegetable drugs as starting materials. This plan is based on the formula \( r = 1.5 \sqrt{N} \), where \( N \) is the number of sampling units. Samples are taken from each of the \( N \) sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory and tested for identity. If the results are concordant, \( r \) samples are randomly selected and individually subjected to testing. If the results are concordant, the \( r \) samples are pooled for the retention sample.

The accompanying table gives the values of \( n, p \) and \( r \) according to the different plans.

<table>
<thead>
<tr>
<th>Value of ( n, p ) or ( r )</th>
<th>Values of ( N )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n ) plan</td>
<td>( p ) plan</td>
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<tr>
<td>----------------------------</td>
<td>------------------</td>
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<tr>
<td>2</td>
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GUIDANCE FOR THOSE PREPARING OR COMMENTING ON MONOGRAPHS FOR PREPARATIONS TO BE INCLUDED IN THE INTERNATIONAL PHARMACOPOEIA

In preparing or commenting upon monographs for inclusion in The International Pharmacopoeia experts are asked to bear in mind the role and objectives of that pharmacopoeia, which have been summarized as follows:

(a) To provide specifications on the purity and potency of essential drug substances, widely used pharmaceutical aids, and dosage forms. These specifications should be adequate to assure the safety and efficacy of these products as well as adequate reproducibility of their effects in clinical use, but they should not be unnecessarily stringent, since this would increase the cost of the products. In the case of recently introduced products, specifications should be developed to ensure compatibility with the samples for which the toxicological properties and clinical efficacy and safety were initially established.

(b) To support such specifications with readily applicable methods of testing and analysis, with attention to the facilities available within control laboratories in developing countries.

(c) To provide general methods of analysis that would be applicable not only to materials included in the pharmacopoeia but also to new products submitted for registration.

(d) To accommodate, where appropriate, a measure of flexibility into methods and requirements that will facilitate the use of The International Pharmacopoeia on a global basis, particularly in connection with dosage forms.

(e) To present all these elements in such a manner that The International Pharmacopoeia, or selected parts of it, can be officially adopted by any Member State of the World Health Organization.
To meet some of these aims guidance concerning monographs for
drug substances has been published.¹ The additional guidelines set
out below refer specifically to monographs for dosage forms.

1. Reference substances should be avoided if this is possible.

2. In cases in which infrared spectrophotometry is regarded as
essential for the appropriate identification of a particular drug
substance in a dosage form, an alternative series of tests should
always be given. Because the process of extraction of the drug
substance from the dosage form may result in a polymorphic change,
appropriate instructions should be given to ensure that the extracted
ingredient is converted to the form on which any reference spectrum
is based.

3. In the alternative series of identification tests it is often useful
to employ thin-layer chromatography (TLC), using the same solvent
system as in the TLC test for related substances. This, however,
requires a reference substance, and it should therefore be invoked
only if it has proved essential to establish a reference substance for
other purposes.

4. It is desirable that at least one colour test should be included
in the identification scheme. The combination of tests proposed
should provide reasonable assurance that the labelled product is
adequately identified.

5. Since The International Pharmacopoeia is intended to provide
an independent challenge to dosage forms and since the analyst
examining such samples may not have recourse to data obtained on
the drug substance used to manufacture the dosage forms, it is
considered desirable that tests should be included in the monograph
for the dosage form to demonstrate freedom from undue quantities
of manufacturing or degradation impurities. Tests for impurities
that may arise in the synthetic process used to manufacture the drug
substance serve to demonstrate that an acceptable quality of that
ingredient has been used to prepare the dosage form. Tests for
impurities that may arise from degradation of the drug substance,
either during preparation of the dosage form or during its storage,
serve to demonstrate appropriate manufacture and storage. It
should be recognized, however, that the limits for impurities arising
from degradation of the drug substance during manufacture of the

¹ WHO Technical Report Series, No. 704, 1984 (Twenty-ninth report of the
WHO Expert Committee on Specifications for Pharmaceutical Preparations),
Annex 5.
dosage form may often need to be less stringent than those for the same degradation that apply to the drug substance itself. Limits for impurities that may arise only during synthesis should, on the other hand, be of similar stringency to those applied to the drug substance itself.

6. Wherever possible, impurities should be sought using TLC (high–low system) by applying a suitable solution prepared from the dosage form at a reasonably high loading and comparing any secondary spots obtained with the principal spot in the same solution, appropriately diluted. Due regard should be paid, however, to the fact that in certain drugs the possible impurities may respond very differently to the system of visualization used. Such problems may be minimized by using, for example, fluorescent plates, which can be examined under an ultraviolet lamp having a maximum output at about 254 nm, or iodine vapours to produce coloured spots. In general, it is desirable to choose a system such that the principal spot shows an $R_t$ value of about 0.5, although in certain cases it can be of advantage if the principal spot remains near the baseline or migrates to the solvent front, provided that secondary spots of interest are well separated.

7. Gas–liquid chromatography or high-performance liquid chromatography (HPLC) should be used only when there is full justification for doing so, i.e., where it is of particular importance to control an impurity and where no other method is reasonably available.

8. Heavy metals tests should be employed only when the dosage of the drug demands it, e.g., when quantities of 0.5 g or more are given per day over a long period, or when some other reason can be identified.

9. Where it is necessary to control the acidity or alkalinity of a preparation, pH measurement should be included if the material has inherent buffering properties; otherwise a titrimetric procedure should be recommended. In general, a test for acidity or alkalinity should be required only when the preparation being tested does not show a marked buffering effect. Such tests are, in general, only required for injectable preparations or for solutions that will come into contact with delicate membranes (such as the eye).

10. Requirements for clarity of solution should, in general, be invoked whenever the preparation, either as such or after solution, is intended to be injected or is for ocular use or when the presence of an opalescence is indicative of the presence of an impurity or of

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degradation. Such a test should not be included in monographs simply for the purpose of controlling the presence of mechanically introduced dirt.

11. The assay procedure employed might be stability-indicating or, if nonspecific, should be supplemented by appropriate limit tests for degradation products. It may be possible to use less accurate methods than would be necessary for the drug substance itself since specifications for dosage forms take into account not only the purity of the chemical product but also the practical facts of industrial manufacture.

12. All tests should, wherever possible, make use of reagents that are already described in The International Pharmacopoeia. Toxic materials such as mercuric salts, benzene, reagents known to be carcinogenic, and other undesirable materials should be avoided.

13. In view of the possible use of The International Pharmacopoeia in tropical areas, care should be taken to minimize the use of very volatile solvents, such as ether. This is of particular importance in devising mobile phases for TLC, since the composition of such phases is liable to change if volatile solvents are included.

14. Existing pharmacopoeial methods should be invoked whenever possible since these will have been examined widely, whereas new suggestions will require verification in other laboratories and the resources for this may not always be readily available.

15. Until tests for microbial contamination are developed a statement should be added to the monographs for materials of natural origin under "Additional information". Attention should be paid to the microbial purity.
LIST OF AVAILABLE INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

1988

General information

International Chemical Reference Substances 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.

Directions for use and analytical data as required for the use intended in the relevant specifications are given in the certificates enclosed with the substances when distributed. More detailed analytical reports on the substances may be obtained on request from the WHO Collaborating Centre for Chemical Reference Substances.

The International Chemical Reference Substances may also be used in tests and assays not described in WHO specifications. However, the responsibility for assessing the suitability of the substances then rests with the user.

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 other storage conditions are required, this is stated on the label or in the accompanying leaflet.

The stability of the International Chemical Reference Substances kept at the Collaborating Centre is monitored by regular re-examination, and deteriorated materials are replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and may be obtained on request.

Ordering information

Orders for the International Chemical Reference Substances should be sent to:

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The International Chemical Reference Substances are only supplied in standard packages as indicated in the following list:

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<th>Package size</th>
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54
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</tr>
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<td>200 mg</td>
</tr>
<tr>
<td>phenoxymethylpenicillin calcium</td>
<td>200 mg</td>
</tr>
<tr>
<td>phenoxymethylpenicillin potassium</td>
<td>200 mg</td>
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<tr>
<td>phenytoin</td>
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<td>prednisolone</td>
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<td>prednisolone acetate</td>
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<tr>
<td>prednisone</td>
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<th>Reference substance</th>
<th>Package size</th>
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<td>procarbazine hydrochloride</td>
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<td>progestosterone</td>
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<td>propicillin potassium</td>
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<td>propranolol hydrochloride&lt;sup&gt;1&lt;/sup&gt;</td>
<td>100 mg</td>
</tr>
<tr>
<td>propylthiouracil</td>
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<tr>
<td>pyridostigmine bromide</td>
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<td>reserpine&lt;sup&gt;1&lt;/sup&gt;</td>
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</tr>
<tr>
<td>sulfanilamide</td>
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</tr>
<tr>
<td>testosterone propionate propionate</td>
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<td>tetracycline hydrochloride</td>
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<td>tolnaftate</td>
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<td>trimethadione</td>
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<tr>
<td>trimethoprim</td>
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<tr>
<td>trimethyguanidine sulfate</td>
<td>100 mg</td>
</tr>
<tr>
<td>tubocurarine chloride</td>
<td>100 mg</td>
</tr>
<tr>
<td>vitamin A acetate (solution) [retinol]</td>
<td>5 capsules&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>warfarin</td>
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<sup>2</sup> About 9 mg in 250 mg of oil per capsule.
Annex 5

WHO CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE

1. RESOLUTION WHA41.18

The Forty-first World Health Assembly,
Taking note of previous resolutions on the question;
Having examined the Director-General’s report on the rational use of drugs, and in particular the proposed amendments to the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce;
Noting the fact that, in any case of obvious doubt, any Member State may request the Organization for assistance in finding an independent collaborating centre to carry out batch tests for the purposes of quality control;
1.adopts the attached revised text of the expanded WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce;
2.invites Member States which are not yet participating in the Scheme to do so;
3.recommends to Member States that they implement as far as possible all the provisions of the expanded WHO Certification Scheme;
4.requests the Director-General to report, in the context of his report on WHO’s revised drug strategy to a future World Health Assembly, on the progress accomplished in the implementation of the expanded WHO Certification Scheme.

[Adopted by the Forty-first World Health Assembly on 13 May 1988]

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2. WHO CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE

Part I—Certification of a pharmaceutical product

1. For the purpose of this Certification Scheme "pharmaceutical product" means any medicine intended for human use, or a veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, when it is subject to control by legislation in the exporting Member State and in the importing Member State. It should be noted that, as a matter of policy, some Member States do not inspect manufacturers of starting materials, while in other countries such inspection is limited to selected active ingredients.

2. A pharmaceutical product exported or imported under this Certification Scheme would be certified by the competent authority of the exporting Member State on a Certificate of a Pharmaceutical Product, issued at the request of the interested party, to be sent to the competent authority of the importing Member State, which would decide to grant or to refuse the authorization for sale or distribution of the certified product, or to make the authorization conditional on the submission of supplementary data.

3. The issue of the Certificate of a Pharmaceutical Product would be subject to the conditions required by the competent authority of the exporting Member State in order to certify that:

   (a) the product is authorized for sale or distribution within the exporting Member State (if not, the reasons therefore would be stated on the certificate); and

   (b) the manufacturing plant in which the product is produced is subject to inspection at suitable intervals to show that the manufacturer conforms to requirements for good practices in manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported.

A suggested layout of a Certificate of a Pharmaceutical Product with explanatory notes is attached.

4. Certification of individual batches of pharmaceutical products and substances is only undertaken exceptionally by the competent authorities of Member States. Even then, it is rarely applied other
than to vaccines and other biologicals. If certificates of individual batches of a product covered by a Certificate of a Pharmaceutical Product are required, such certificates could be issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of a Pharmaceutical Product, and a statement that the batch conforms either to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, as the case may be, to published specifications, or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis and on stability, and other information such as an approved technical summary of the data regarding safety and efficacy on which the domestic marketing authorization is based.

Part II—Exchange of information

1. Upon the request of the competent authority of the Member State into which a pharmaceutical product covered by this Certification Scheme is to be or has been imported, the competent authority of the exporting Member State should provide:

(a) information on the implementation of the Requirements for Good Practices in the Manufacture and Quality Control of Drugs as recommended by the World Health Organization;¹
(b) information on controls of the product as exercised by the competent authority of the exporting Member State;
(c) the names and functions of the persons designated to sign certificates of individual batches of the product to be exported;
(d) copies of all information and labelling supplied with the product, as provided on packaging materials and package inserts, and whether directed to the prescriber or the patient, that have been approved by the competent authority in the exporting

¹ It is realized that in some countries this may require the consent of the manufacturer.
Member State, together with the date(s) on which such approval was accorded.

Information on general and specific standards for quality control of the product to be exported, in so far as they are required to comply with legislative provisions of the importing Member State, could also be supplied with the consent of the manufacturer.

2. In the case of quality defects of products imported under this Certification Scheme that are considered to be of a serious nature by the importing country, not attributable to local conditions and circumstances, and appearing after the introduction of a particular batch into the importing Member State, the competent authority should notify the occurrence, together with the relevant facts, to the competent authority of the exporting Member State that had issued the Certificate for the product concerned, with a request to institute inquiries. Conversely, if the competent authority of the exporting Member State ascertains serious quality defects, that competent authority should notify the competent authority of the importing Member State.

Part III—Participating Member States

1. Each Member State agreeing to participate in the Certification Scheme shall communicate (a) the name and address of its principal authority to be considered as competent within the meaning of the Certification Scheme, and (b) any significant reservations relating to its participation, to the Director-General of the World Health Organization, who would notify all other Member States.

2. Exporting Member States participating in the Certification Scheme shall ensure that:

(a) authorization for sale or distribution of pharmaceutical products is subject to appropriate testing measures, by the competent authority, designed to ensure their quality and stability, and that adequate laboratory facilities are available for this purpose;

(b) the pharmaceutical industry is obliged to conform to requirements for good practices in the manufacture and quality control of drugs as recommended by the World Health Organization;

(c) the competent authority is empowered to conduct appropriate investigations to ensure that manufacturers conform to the
requirements referred to in (b), including, for example, the examination of records and the taking of samples;
(d) the inspectors in the services of its competent authority have appropriate qualifications and experience.

3. Exporting Member States participating in the Certification Scheme should, whenever possible, ensure that the international nonproprietary names, whenever available, are used in the description of the composition of the product on the Certificates and, as far as possible, appear on the labelling of pharmaceutical products to be exported under the Certification Scheme.
CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Name and dosage form of product: ..........................................................................................................

Name and amount of each active ingredient: ...........................................................................................

Manufacturer, and/or when applicable, the person responsible for placing the product on the market: ............... 

Address(es): ...........................................................................................................................................

It is certified that:

☐ This product has been authorized to be placed on the market for use in this country.

☐ Number of permit and date of issue (if applicable): .................................................................................

☐ The enclosed documents constitute the complete text of all labelling and prescribing information which is
   authorized for use in this country.

☐ This product has not been authorized to be placed on the market for use in this country for the following reasons:

..............................................................................................................................................................

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported.

(See Explanatory Notes.)

..............................................................................................................................................................

(Signature of designated authority) .......................................................... (Place and date)

1 This certificate is intended to be product-specific. The approved information for different dosage forms of the same active substance frequently differs in fundamental aspects. Confusion will inevitably arise if information relating to different products, or even different dosage forms, is attached to the same certificate.

2 Use, where possible, international nonproprietary names (INN) or national nonproprietary names.
Explanatory Notes

Certificate of a Pharmaceutical Product

This certificate is intended to define the status of the pharmaceutical product and its manufacturer in the exporting country. It is issued by the competent authority in the exporting country in accordance with the requirements of the competent authority of the importing country. It may be required by the importing country at the time of the first importation and subsequently if confirmation or updating is required.

The requirements for good practices in the manufacture and quality control of drugs mentioned in the certificate refer to the text adopted by the Twenty-eighth World Health Assembly in its resolution WHA28.65 (see Official Records, No. 226, Annex 12, Part 1).

Batch certificates

Certification of individual batches of a pharmaceutical product or substance is only undertaken exceptionally by the competent authorities of Member States. Even then, it is only rarely applied other than to vaccines and other biologicals. If certificates of individual batches of products covered by a Certificate of a Pharmaceutical Product are required, such certificates could be issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of a Pharmaceutical Product and a statement that the batch conforms either to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, where appropriate, to published specifications or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis, stability data, and other information such as an approved technical summary of the data regarding safety and efficacy on which the domestic marketing authorization is based.
Annex 6

GUIDING PRINCIPLES FOR SMALL NATIONAL DRUG REGULATORY AUTHORITIES

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1 Based on the report of a meeting convened by WHO in November 1987, with
the following participants: Mr J. Y. Binka, Medicines Board, Medical and Health
Department, Banjul, The Gambia; Dr J. L. Carrois, Cabinet International Carrois,
Paris, France; Dr H. El-Sheikh, Ministry of Health, Khartoum, Sudan; Dr
G. Lewandowski, Ciba-Geigy Ltd, Basle, Switzerland; Mr L. Preucod, Barbados
Drug Service, St Michael, Barbados; Professor M. D. Rawlins, Department of
Pharmacological Sciences, University of Newcastle-upon-Tyne, Newcastle-upon-
Tyne, England; Mr J. Ruberantwari, Ministry of Health, Entebbe, Uganda; Dr P. N.
Suwal, Ministry of Forest and Soil Conservation, Kathmandu, Nepal; Mr Tan Kiok
K'ng, Pharmaceutical Department, Ministry of Health, Singapore; Mrs S. S. Tseuma,
Office of the Chief Pharmacist, Nairobi, Kenya.

2 This text, which remains a consultative document, has also been published,
since its review and endorsement by the Expert Committee in November–December
1. GENERAL CONSIDERATIONS

Small countries which have yet to introduce comprehensive legal provisions for drug regulation can draw from a diversity of national systems in determining their own requirements. None the less, problems in establishing drug control in developing countries have too often resulted from the adaptation of provisions successful elsewhere but of a complexity that precludes their effective implementation in the country of adoption. It is of paramount importance that legislation and administrative practices are attuned to available resources and that every opportunity is taken to obtain and use information provided by regulatory authorities in other countries on pharmaceutical products and substances moving in international commerce.

Channels of communication between national regulatory authorities are improving, as is evident from the information contained in WHO's monthly Pharmaceuticals newsletter, the quarterly journal WHO drug information, and the United Nations Consolidated List of Products Whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments. Moreover, many difficulties inherent in storing, retrieving and analysing data that subserve the many facets of the regulatory process can now be overcome by the use of microcomputers and commercial software packages.

1.1 The scope of drug control

To be effective, a small drug regulatory authority needs to operate within the context of a defined national drugs policy and to interrelate with other interested bodies, including organizations responsible for drug procurement in the public sector and the national formulary committee, where such exists.

1.2 Basic responsibilities

The responsibilities of the regulatory authority are to ensure that all products subject to its control conform to acceptable standards of quality, safety and efficacy; and that all premises and practices employed to manufacture, store and distribute these products comply with requirements to ensure the continued conformity of the products to these standards until such time as they are delivered to the end-user.
1.3 Licensing functions

These objectives can be accomplished effectively only if a mandatory system of licensing products, manufacturers, importing agents, and distributors is in place. A small authority has strictly limited capacity to undertake these tasks. For the assurances it requires in relation to imported pharmaceutical products and drug substances, it is vitally dependent on authoritative, reliable, and independent information generated in the exporting country. This information is most effectively obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Before a formal licensing system can become operative, it is necessary:

(a) to adopt a precise definition of a drug product and of the various categories of licence-holders;

(b) to determine the content and format of licences, both for products and for licence-holders;

(c) to detail the criteria on which licence applications will be assessed; and

(d) to provide guidance to interested parties on the content and format of licence applications, and on the circumstances in which an application for renewal, extension or variation of a licence will be required.

The definition of a drug product is commonly contingent upon the claims that are made for it. Ideally, controls need to be applied to any product that is offered for sale for administration to human beings for treating, preventing and diagnosing disease, for anaesthesia, for contraception, and for otherwise altering normal physiological functions. In practice, exemptions may need to be granted to various specific categories of products in order to address priorities effectively. It might be decided as an interim measure, for example, to require licences only for products listed in a national formulary. Ultimately, however, control needs to be extended not only to all products moving in the major distribution channels, but to those formulated in pharmacies and hospital dispensaries, to

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1 Veterinary products administered to food-producing animals may also fall into this category; see the revised WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (WHO Technical Report Series, No. 790, 1990, Annex 5).
herbal preparations, and to other traditional medicines entering into local commerce.

Analogous priorities may also need to be accorded to the registration of licence-holders, although the ultimate objective should be to embrace all manufacturers, importing agents, wholesalers involved in repackaging, pharmacies, and hospital dispensaries in a system that imposes upon them relevant statutory obligations.

1.4 Product licences

The issuance of product licences is pivotal to any system of drug control. The licence is a legal document that establishes the detailed composition and formulation of the product, the pharmacopoeial or other officially recognized specifications of its ingredients, its clinical interchangeability (in the case of multisource products), and its packaging, shelf-life and labelling. Of itself, this goes a long way towards establishing the assurances of quality, efficacy, and safety to which the system is directed. However, without a viable pharmaceutical inspectorate or access to an independent quality-control laboratory operating to standards that will ensure its credibility in the event of dispute, licensing provisions cannot be effectively enforced.

1.5 Manufacturers' and distributors' licences

The pharmaceutical inspectorate is responsible for ensuring that pharmaceutical products comply with conditions set out in the licence up to the time that they are delivered to the end-user. Its functions are:

(a) to establish, through periodic formal inspections and spot-checks, that all categories of licence-holder are operating in accordance with their licensed activities, prevailing standards of good manufacturing practice, and other prescribed regulations;

(b) to maintain oversight of distribution channels, either by inspection and monitoring or by arranging for pharmacopoeial analysis of selected samples, with a view to ensuring that products are not subject to unacceptable degradation during transit and storage at the periphery.
1.6 New drug assessments

Within highly evolved national drug regulatory authorities much effort is directed to establishing the efficacy and safety of new drug entities through pharmaceutical, biological, and clinical assessment and through subsequent surveillance of their performance in routine use after marketing. Premarketing assessment is dependent upon detailed multidisciplinary technical review, and postmarketing surveillance requires a highly developed health care infrastructure. Only in exceptional circumstances should a small regulatory authority contemplate allocation of scarce resources to these ends. Reliance must be placed primarily on information notified by other countries through the network of national information officers established by WHO.

1.7 Authorization of clinical trials

A small authority may occasionally need to consider an application to conduct a clinical trial of an unregistered drug in the treatment of a condition that has a high local prevalence. To provide for this contingency, the registration system should include provision for the importation of the necessary materials, subject to appropriate controls. Such trials should only take place after formal clearance has been obtained from the competent registration authority and after assurances have been obtained that they will be conducted in conformity with the principles contained in the World Medical Association's Declaration of Helsinki and the Proposed International Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences.1 WHO stands ready to offer independent technical advice to national authorities in these circumstances.

1.8 Terms of reference of the regulatory authority

The formal terms of reference of a national drug regulatory authority are determined by statute and regulation. Legislation relating to pharmaceutical products has developed piecemeal in many countries, and there are obvious advantages in bringing

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matters concerned with their regulation under one law. For example, it is important to correlate laws relating to the control of narcotic and psychotropic substances with requirements for product registration. If comprehensive overhaul of the legal system is impracticable, control within the existing framework through regulations specifically related to the registration of pharmaceutical products offers advantages of economy and time-saving. Whichever option is chosen, regulatory authorities require the flexibility to respond to changing circumstances imposed by the evolution of pharmaceutical science.

In general terms, the authority should be vested with legal powers to:

(a) issue, vary and revoke licences for pharmaceutical products on grounds of quality, safety, and efficacy;
(b) secure the subsequent safe and effective use of each product by controlling, through the terms of the licence, the content of all labelling (including package inserts, associated prescribing information and advertising) and the channels through which the product may legitimately be supplied; and
(c) inspect and license all manufacturing premises, importing agents, wholesalers and distributors, hospital dispensaries, independent pharmacies, and other retail outlets to ensure that they comply with prevailing regulations and guidelines.

1.9 Powers of enforcement

In order to implement these responsibilities the authority must command powers of enforcement backed by legal provision for penal sanction against offenders.

In establishing administrative mechanisms for decision-making, the regulatory authority should not lose necessary flexibility. In particular, it should make provision for:

(a) implementing decisions regarded as urgent in the interest of public safety; and
(b) formal consultation (usually through representative bodies) with pharmaceutical companies and other interested parties, including pharmacists, doctors, nurses, and patients.
1.10 Technical competence

A small licensing authority will rarely, if ever, undertake comprehensive independent assessments of the safety and efficacy of individual products. The administrative and technical responsibilities that fall within its ambit are essentially of a pharmaceutical nature and they are directed primarily to quality assurance. The professional staff must include members with a thorough understanding and practical experience of the different facets of this work.

The responsible officer is accountable for the professional validation and assessment of licence applications and for the administrative aspects of licensing and, as such, should be involved in determining priorities and developing a timetable for implementation of controls. These activities require administrative and clerical support and premises sufficient to handle the large volume of documentation involved with appropriate confidentiality. Efficiency of operation is enhanced when the required information can be retrieved rapidly from a computerized data base.

1.11 Advisory bodies

The responsible officer must also have access to a standing advisory committee or board of independent experts (including academic and practising health care professionals) for advice on technical issues. Consideration should also be given to the need for a multidisciplinary commission to advise on matters of general policy and administration and to ensure effective relations with bodies responsible for drug procurement in the public sector and with the national formulary committee.

1.12 Independence of operation

To retain public confidence and respect, the authority must be seen to undertake its tasks in an independent, authoritative, and impartial manner. It should be concerned exclusively with the determination of standards and the implementation of controls. Although it will need to work closely with the authority responsible for drug procurement within the public sector, it should not itself be responsible for procurement and it should remain independent and autonomous in its operational activities and decisions.
2. ADMINISTRATIVE ASPECTS OF THE LICENSING PROCESS

2.1 Provisional registration of existing medicinal products

Before any system of control can become effective, it is necessary to identify and catalogue all products already sold or otherwise supplied on the domestic market, in both the public and the private sectors, that qualify for control. To this end, all manufacturers and importing agencies must be given reasonable notice through official gazettes, the trade press and other media of their obligation to notify the authority by a specific date of all medicinal products that they currently distribute within the jurisdiction of the authority and that they intend to continue to supply after a duly appointed day, on which licensing requirements enter into operation. After the appointed day no medicinal product may lawfully be distributed or supplied unless its existence has been notified to the authority, and no new product may be introduced until a request for a product licence has been granted by the authority.

Effective administration of the provisional registration procedure is dependent upon:

(a) prior identification of all interested manufacturers and importers;
(b) a precise definition of a notifiable medicinal product based primarily on the labelled claims and the indications for use;
(c) the issuance of guidelines on the procedure to be followed.

Each notified product must be identified by name (either brand or generic), the names and full addresses of the manufacturer and importing agent, a description of the dosage form, its composition — including active and inactive ingredients (using international nonproprietary names where appropriate) — the therapeutic class, the indications, a copy of all labelling, including any package insert, and a copy of any relevant certificates and warranties relating to the product or its components.

2.2 Screening of provisionally registered products

A rapid screening of notified products should be undertaken at the earliest opportunity with a view to securing the withdrawal of any products which, simply on the basis of a review of their
ingredients and indications, are judged not to meet admissible standards of safety. This may be achieved by the withdrawal of permission to trade in specific notified products or the issuance of regulations imposing specified restrictions on precisely defined groups of products.

After this preliminary review, a set of longer-term priorities needs to be set for the definitive assessment of provisionally registered products. Consideration needs to be given to the resources required, both in manpower and information, if the review is to be adapted to a proposed time-schedule. Standards must be maintained and calls to accelerate the speed of implementation must be recognized as having resource implications.

In planning priorities, consideration must be given to:

(a) the number of provisionally registered products to be processed;
(b) the number of staff and/or consultants to be allocated to the task;
(c) the amount of relevant information available from other national authorities;
(d) the extent to which products can be reviewed in groups rather than individually;
(e) the extent to which a laissez-faire disposition can be adopted towards such products as herbal remedies and tonics that are without potent pharmacological activity and carry imprecise claims, but which satisfy an acknowledged public demand.

Considerations of safety require that particular attention be accorded to:

(a) products that either have been withdrawn or are the subject of restrictive regulatory action in other countries as notified in the United Nations Consolidated List of Products Whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments, and in WHO’s Pharmaceuticals newsletter to national drug regulatory authorities;
(b) products representing examples of irrational poly-pharmacy;
and
(c) products for which exaggerated or spurious promotional claims are made in the labelling.

Subsequently, the review needs to be extended in a phased manner, giving priority to drugs that are widely used, listed in
nationally recognized formularies, or of a particularly important therapeutic class. An adequate documentation and information retrieval system is vital for this purpose.

Some traditional products and particularly herbal preparations, because of their complexity, do not lend themselves to licensing on a product-specific basis. Control is then more readily applied through consideration of individual ingredients. Several regulatory authorities have devised administrative approaches to their licensing which are based on a three-category system of classification:

(a) all herbal ingredients, save for those items classified under (b) below, which may be dispensed for a specific, named patient by practitioners of herbal medicine who do not possess a formal medical qualification;

(b) ingredients such as digitalis leaf and atropine which, because of their pharmacological potency or their toxicity, need to be subjected to prescription control; and

(c) ingredients which, as a result of widespread, long-established and apparently innocuous traditional usage, are included, often within defined permissible limits, in labelled products for which limited claims are made and which are sold directly to the public from retail outlets other than pharmacies.

2.3 New product licences

No product that is first proposed for authorization after the appointed day (see section 2.1 above) should be accorded a product licence without first having been submitted to technical assessment. Such products may not necessarily contain a new active ingredient: they may constitute a new combination of two or more established substances or they may merely represent a new dosage strength, a new dosage form, or a generic version of a pre-existing, nominally equivalent licensed product. In no case should the requirement for assessment be waived. A rationale for the formulation of every new product should invariably be provided, but the extent of the required review will vary considerably according to circumstances.

The normal procedure for the authorization of a product is accomplished in three stages:

(a) the application is received from the manufacturer and is checked and assessed for completeness by the authority's technical staff;
(b) it is submitted to the competent standing committee for advice on whether or not to authorize marketing of the product;

(c) the formal administrative action to grant or refuse a licence and to settle its content is then taken by the authority.

The assessment of the product must be based primarily on its safety, quality, and efficacy, with regard to its intended use. In accordance with locally determined requirements, the assessment might also impinge upon comparative efficacy and/or safety and embrace economic factors, including price, cost-effectiveness, and other considerations determined by national policy.

For administrative convenience, the product licence should be as simple as possible. It should always describe the product by name, manufacturer and importing agent, identify the ingredients, (preferably by their international nonproprietary names), and provide full details of the dosage form. It should also contain a serial number, the date of issuance of the licence, its date of expiry, and any special conditions to be observed. It is advisable to cite certain additional items in the licence for easy reference, such as shelf-life and sales category; but in other particulars it should refer to the information submitted by the licence-holder in the dated product application.

2.4 Renewal and variation of licences

Licences should never be regarded as immutable. Ideally, they should be reviewed at, say, five-year intervals. However, many national authorities do not have the capacity to undertake this task, particularly for as long as they remain engaged in the initial review of provisionally licensed products. In these circumstances many products fall to review on an ad hoc basis. Sometimes this is inspired by recently generated concern regarding safety. More frequently, a product attracts attention because the licence-holder has altered the formulation in some way—by changing, for instance, the source of the starting materials, the nature of the excipients, the route of synthesis of an active ingredient, or the claims made in labelling and promotional material. The precise circumstances in which licence-holders are required to apply for variations in a product licence differ from country to country. These circumstances should be clearly defined in all product licence documents, including provisional licences.
Licence-holders should be required, in all circumstances, to inform regulatory authorities immediately of unanticipated adverse effects that could possibly be associated with a licensed product and that might call for restrictive licensing action or the withdrawal of the product licence.

3. TECHNICAL ASPECTS OF THE LICENSING PROCESS

3.1 General considerations

Although countries vary in their resources and priorities, advantage accrues from harmonizing documentary requirements to the fullest possible extent, since this simplifies registration procedures and reduces costs.

The most important starting-point for imported products is the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.¹ This gives basic information on composition, an assurance that the product is manufactured in accordance with good manufacturing practices in premises subject to inspection, and information on the regulatory status of the product in the country of export. A certificate, issued in compliance with the model format recommended by WHO, should be required whenever application is made to license an imported product.

3.2 Products containing long-established chemical entities

For products indicated for standard uses and that contain established ingredients, the following elements of information usually suffice as the basis both for a product licence and for a computerized data retrieval system:

—name of the product
—active ingredient(s) [by international
  nonproprietary name(s)]
—type of formulation
—therapeutic category
—quantitative formula (including excipients)
—quality control specifications
—indications, dosage, method of use

—contraindications, warnings, precautions
—bioavailability data (in vitro/in vivo)
—stability data, shelf-life
—container, packaging, labelling
—intended method of distribution:
  —controlled drug; prescription item
  —pharmacy sale; general sale
—manufacturer
—importer/distributor
—regulatory status in the exporting country.

If the dosage form is a novel one, such as a delayed-release tablet, or if a new route of administration is proposed, supporting data from clinical studies will be required.

3.3 Products containing new chemical entities

Considerably more extensive information is required to support a marketing application for a new drug substance in order to provide assurance of efficacy and safety as well as of quality. In particular, detailed accounts are required of:

(a) chemistry (structure, physical properties, synthesis, specification, impurities, stability characteristics);
(b) pharmacological properties (in animals, in humans);
(c) toxicological data (short and long-term studies in animals, including carcinogenicity studies);
(d) reproductive and teratological studies in animals;
(e) clinical studies.

Small regulatory authorities need to adopt caution in licensing newly developed products because they are likely not to possess the capacity to undertake the multidisciplinary assessment applied to them within large, highly evolved authorities, or to monitor their performance in use through postmarketing surveillance.

In general, a small authority is best advised to wait until this information has been generated and assessed elsewhere before authorizing such a product for use.

In the case of products intended exclusively for tropical parasitic diseases, much of this evidence may need to be built up in countries with limited resources. The expertise of the World Health Organization is at hand to offer advice in these circumstances. Once a decision is taken to authorize such a product for general use, the regulatory authority and the manufacturer share a responsibility to ensure that a monitoring mechanism is put in place to detect
unanticipated reactions. A mutually acceptable plan for postmarketing surveillance should be settled in advance and included in the product licence as a condition of approval.

3.4 Herbal products

The use of herbal and other naturally occurring substances is part of the fabric of traditional medicine. Because of the complex, and sometimes imprecise nature of the ingredients they contain and the paucity of scientific information on their properties, products containing these substances, often in combination, can rarely be reviewed on a rigorously scientific basis. Where time-honoured practices do no apparent harm, there is no urgency for regulatory intervention other than to set up a system for provisional registration.

However, prolonged and apparently uneventful use of a substance offers insecure testimony of its safety. In a few instances, recently commissioned investigations of the potential toxicity of naturally occurring substances widely used as ingredients in these preparations have revealed a previously unsuspected potential for systemic toxicity, carcinogenicity and teratogenicity. Small regulatory authorities need to be quickly and reliably informed of these findings. They should also have the authority to respond promptly to such alerts, either by withdrawing or varying the licences of registered products containing the suspect substance, or by rescheduling the substance in order, for instance, to disallow its use by practitioners who are not medically qualified.

All regulatory authorities should also be alert to the practice of incorporating potent pharmacologically active compounds, such as steroids, into herbal preparations. When this is done clandestinely, it is a manifestly dangerous practice which demands immediate withdrawal of the products and a review of the manufacturer's licence.

3.5 Combinations of potent, therapeutically active substances

The justifications for formulating fixed combinations of potent, therapeutically active substances are few. All biologically active substances have a potential to induce harm as well as therapeutic benefit. The administration of two or more such substances, rather than one, increases the potential for adverse effects. Fixed-ratio
combination products are consequently acceptable only when the
dosage of each ingredient meets the requirements of a defined
population group and when use of the combination provides a clear
advantage over separate administration of the individual active
compounds, in either therapeutic effect or compliance, or when it
enhances safety—as in the case of multiple chemotherapy intended
to reduce the emergence of resistant pathogens.

3.6 Generic products

In many countries, for reasons of economy, drugs destined for use
in the public sector are purchased on open tender. This favours the
use of generic products, and the practice in some countries is for
tenders to be issued, bids examined, and contracts offered by the
procurement authority without reference to the drug regulatory
authority.

The licensing of generic products poses a challenge to all
regulatory authorities, particularly when the product to be supplied
is not registered in the country of origin. The need for expert
assessment is accentuated because not all drug-exporting countries
submit drugs intended exclusively for export to the same rigorous
controls as drugs intended for the domestic market. Nominal
equivalent generic products should contain the same amount of the
same therapeutically active ingredients in the same dosage form and
they should meet required pharmacopoeial standards. However,
they are not necessarily identical and in some instances their clinical
interchangeability may be in question. Differences in colour, shape
and flavour, while obvious and sometimes disconcerting to the
patient, are often inconsequential to the performance of the product,
but differences in sensitizing potential due to the use of different
excipients and differences in stability and bioavailability have
obvious clinical implications. Regulatory authorities consequently
need to consider not only the quality, efficacy and safety of such
products, but also their interchangeability one with another and with
the original innovative product. This concept of interchangeability
applies not only to the dosage form but also to the instructions for
use and even to the packaging specifications, when these are critical
to stability and shelf-life.

Some highly evolved authorities require that every generic
product must satisfy three sets of criteria of therapeutic equivalence.
These relate to:
(a) manufacturing and quality control;
(b) product characteristics and labelling; and
(c) bioequivalence.

Others adopt a more pragmatic approach to the need for experimental demonstration of bioequivalence. Study of the bioavailability of a dosage form is a costly undertaking that is demanding of human resources. It is clearly not a cost-effective requirement for highly water-soluble substances, when neither precise dosage nor consistency of response is a critical consideration. In developing countries the in vivo bioavailability testing of all domestically manufactured products would be impractically costly. The regulatory authority should be in a position to help local manufacturers by advising them on drugs that pose potential bioavailability problems.

In the case of imported products, assurance should be obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce that the product has been produced in accordance with WHO's standards of good manufacturing practices and that, in the light of a full assessment, it has been authorized to be placed on the market in the country of origin.