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# **WHO Expert Committee on Specifications for Pharmaceutical Preparations**

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Twenty-ninth Report

World Health Organization  
Technical Report Series  
704

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World Health Organization, Geneva 1984

ISBN 92 4 120704 3

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PRINTED IN SWITZERLAND

84/6071 – Schöler SA – 7000

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PHARMACEUTICAL PREPARATIONS

Geneva, 5-10 December 1983

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# **WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS**

## **Twenty-ninth Report**

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 5 to 10 December 1983. The meeting was opened on behalf of the Director-General by Dr Lu Rushan, Assistant Director-General, who stressed the need for a realistic approach to quality control of drugs in developing countries. Although the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce provides valuable assurance to these countries on the quality of imported products, the responsible authorities also need to be in a position to check for themselves the quality of these products. As yet, however, many developing countries do not have suitable laboratory facilities.

In its policy of according preference in the International Pharmacopoeia to classical methods of analysis wherever these can be accepted without lowering of standards, the Committee has previously shown itself sensitive to the need to bring a measure of quality control within the grasp of all countries. By now providing, in this report, recommendations on the design of a modest national quality control laboratory, the Committee offers health administrations in those countries still lacking any appropriate facility a valuable guide to the scale of investment required.

### **1. NATIONAL LABORATORIES FOR DRUG SURVEILLANCE AND CONTROL**

Every national government allocates a substantial proportion of its total health budget to drugs. This proportion tends to be greatest in developing countries where it may exceed 40%.

Without assurance that these drugs are relevant to priority health needs and meet acceptable standards of efficacy and safety, the efficiency of any health service is evidently compromised. In highly developed countries considerable administrative and technical effort

is directed to ensuring that patients receive effective drugs of good quality. It is crucial to the objective of health for all by the year 2000 that a reliable system of drug control be brought within the grasp of every country.

This need calls for the institution of a national drug registration system embodied within a legislative framework that, *inter alia*, contains provisions to assure the quality of all registered products. These provisions must take cognizance of the various ways in which substandard products may arise. The three principal ways are:

—products that initially conform to prescribed specifications may deteriorate before they are used as a consequence of inappropriate formulation, packaging, or storage conditions; this may result in loss of activity and exceptionally in the formation of toxic degradation products;

—failure to institute and maintain good manufacturing practices may result in errors of formulation or labelling;

—illicitly manufactured drugs, which may be substandard or even spurious, may enter the distribution chain.

To be self-sufficient in meeting these contingencies a country must enforce a system of control that provides for:

—regular inspection of all production units to ensure that good manufacturing practices, as exemplified in the code of *Good practices in the manufacture and quality control of drugs* promulgated by WHO (1) are maintained;

—spot checks of the quality of all products in the distribution chain through carefully planned sampling programmes.

An account of the various elements of quality assurance in pharmaceutical supply systems is contained in the Committee's twenty-seventh report (2). Full implementation of these measures requires both extensive laboratory facilities and a well staffed inspectorate. It is evident, however, that in many countries resources are not available to provide for investment on this scale.

For these countries, the WHO "Certification scheme on the quality of pharmaceutical products moving in international commerce" (1, p. 94), offers some safeguard insofar as imported products are concerned. The scheme provides assurance, underwritten by the drug regulatory authority in the country of origin, that a specific product has been manufactured within

premises that are regularly inspected and that conform to internationally recognized standards of operation.

However, the WHO certification scheme has no relevance to locally manufactured products; it provides no safeguard that an initially acceptable product will not deteriorate owing to improper storage; nor does it apply when a product is imported from a trading company located outside the country of original manufacture. In the last two instances it is particularly important to evaluate quality by appropriate analyses of the finished product.

Consequently, every country, regardless of its stage of development, should consider the need for investment in an independent national drug quality control laboratory. The recommendations contained in Annex 1 are directed to the many developing countries that have not as yet created such a facility and that do not command the resources to maintain a comprehensive system of control.

It should be recognized, in particular, that:

— simple procedures, such as tablet disintegration tests, are frequently of critical importance in eliminating seriously substandard preparations;

— a small laboratory directed by a competent, discerning individual will provide a persuasive deterrent to negligent or fraudulent manufacturing or importing practices;

— the availability of complex automated equipment accelerates but does not necessarily raise the standard of analytical work. Moreover, such equipment performs reliably only when it is expertly maintained and its operation may require the use of highly purified and expensive reagents.

## **1.1 Proposed model laboratories**

### *Staffing and physical facilities*

Recommendations on the staffing and organization of two model laboratories for developing countries where no facilities exist are provided in Annex 1. No concession is made in these recommendations towards any relaxation of standards. Even the smaller of the model laboratories provides for the full analysis of more than 75% of WHO's model list of essential drugs (3) in accordance with the methods provided in *The international pharmacopoeia* (4).

Emphasis is placed upon economy, both of scale and equipment. None the less, it is recognized that efficient temperature and humidity control is imperative in laboratories located in tropical regions, notwithstanding the high capital expenditure and maintenance costs involved and the heavy energy demands. Several analytical techniques (including infrared spectrophotometry) do not provide reliable results in a hot and humid environment which, moreover, promotes corrosion and accelerates deterioration of expensive instruments.

Having regard to the limited opportunity for institutional technical training in developing countries, newly recruited staff will generally require a period of in-service training in a laboratory adapted to their educational background, individual aptitude, and assigned responsibilities.

#### *Good control laboratory practices*

The Committee reiterated the request made in its twenty-eighth report (5) that guidelines on good control-laboratory practices be elaborated to embrace various aspects of the management of a national drug control laboratory, including advice on sampling procedures.

#### *Legal status*

Regardless of the facilities available, the reliability of any analytical laboratory is vitally dependent upon the calibre and experience of its director. A national quality control laboratory has onerous responsibilities that demand reliable judgements: if the need arises, decisions must withstand examination in a court of law.

Because of the legal connotation of the analytical work undertaken in control laboratories, a special status should be accorded by statute to analytical reports issued by them. Such a privilege, which should however remain open to challenge in defined circumstances, will facilitate the resolution of disputes should reports ever be contested by interested parties.

To avoid possible conflicts of interest, a national laboratory should not engage in routine testing of samples at the request of individual pharmaceutical manufacturers. It is, however, an important function of the laboratory to advise the manufacturers on means of improving their quality control procedures.

### *Complementary arrangements*

Although the capacity of these model laboratories is limited, the measure of self-sufficiency that they provide means that the concept of using intercountry regional testing facilities as referral laboratories for more difficult analyses becomes a viable possibility.

The Committee recognized the continuing importance of the service provided by WHO to national administrations in developing countries in arranging for the independent analysis of drug samples on a contractual basis by quality control laboratories in other countries. It recommends that a short guide to the scheme be prepared to describe the associated legal and financial considerations, the nature of the samples required for analysis, and the supplementary information required, including the precise reason for the request.

## **2. THE INTERNATIONAL PHARMACOPOEIA**

### **2.1 Current status of work**

With the completion of volume 3, the third edition of *The international pharmacopoeia*, of which volumes 1 and 2 have already been published (4), will provide monographs for almost all drug substances included within the WHO Model List of Essential Drugs as revised in December 1982 (3).

### **2.2 Monographs for individual dosage forms**

The next step in the development of the third edition of *The international pharmacopoeia* will be to determine the extent to which specifications of a general or specific nature for medicinal dosage forms can be provided. This will have immediate relevance to WHO's Action Programme on Essential Drugs and to countries mainly dependent upon the importation of finished products.

As a preliminary measure, some revision of the existing general monograph on solid dosage forms will be required (2). In particular, a review of the status of dissolution testing is needed with the objective of developing a relevant test for inclusion in *The international pharmacopoeia*.

The importance of dissolution testing of solid dosage forms, and particularly tablets, is now widely appreciated. However, such tests

generally have to be undertaken on a selective basis in view of their cost and time-consuming nature. WHO was accordingly requested to consult the appropriate experts and to prepare a position paper on both the methodology of dissolution testing and the principles that should be applied to the selection of products and dosage forms to be tested. The Committee hoped that these proposals would be available for presentation to its next meeting, together with general guidelines on extraction and separation procedures for the testing of solid dosage forms, as requested in the Committee's twenty-eighth reports (5).

### **2.3 Quality requirements for pharmaceutical aids**

In its twenty-eighth report (5), the Committee recommended that volume 4 of the third edition of *The international pharmacopoeia* should contain monographs on excipients and other substances required in the formulation of finished products (collectively termed pharmaceutical aids). On occasion, the quality requirements for pharmaceutical aids may involve considerations that are not normally applied to drug substances. The main points to be considered are set out in Annex 2 of this report.

In selecting pharmaceutical aids for inclusion in *The international pharmacopoeia*, priority will be given to those that are generally available in both developed and developing countries. Colouring matters and flavours will be excluded, pending further consideration, having regard to the difficulty of obtaining a global consensus.

A number of pharmaceutical aids, both naturally-occurring and synthetic in origin, are, in fact, mixtures and not homogeneous substances. Moreover, various combination products exist in commerce, including ointment and suppository bases, which consist of several components that are selected to achieve optimum properties for a specific purpose. Products in this latter category will not, at present, be considered for inclusion in *The international pharmacopoeia*.

Technical information on the properties of pharmaceutical aids has hitherto been dispersed among various published sources, including manufacturers' data sheets. However, two national pharmaceutical societies (the US Academy of Pharmaceutical Sciences and the Pharmaceutical Society of Great Britain) are now collaborating to publish a comprehensive compendium of such information.

## 2.4 The use of alternative methods of analysis

Alternative tests for identification are included in *The international pharmacopoeia* and in a number of national pharmacopoeias. These permit the use of classical tests in place of physicochemical tests requiring expensive apparatus. Users of monographs may also legitimately develop alternative assay methods not included in the pharmacopoeia, subject to validation. Thus, a specific high-pressure liquid chromatographic method might be used instead of a nonspecific titrimetric method supported by a thin-layer chromatographic test for impurities.

However, in every instance the analytical procedures described in the relevant pharmacopoeia must be regarded as binding in the case of legal dispute.

## 2.5 Pharmacopoeial monographs—advice to reviewers of drafts

To ensure consistency of comments and suggestions by reviewers of draft monographs, a set of guidelines has been drawn up that defines the characteristics and functions of *The international pharmacopoeia* (Annex 5). These guidelines relate specifically to drug substances, and a complimentary set of criteria will now be established for monographs on dosage forms.

The existing guidelines will also be expanded to emphasize the need to exclude the use of toxic metal reagents and toxic solvents. As a matter of priority, consultations will be put in hand to identify appropriate alternative procedures whenever toxic reagents are at present required in a proposed test procedure (such as the use of mercuric acetate in some nonaqueous titrations).

## 2.6 Review of published monographs

All published pharmacopoeial monographs should be kept under review and modified as necessary to accommodate improved analytical procedures, or newly introduced methods of synthesis of drug substances. Accordingly, the possibility will be explored of enlisting help from a network of collaborating laboratories to ensure that the monographs of *The international pharmacopoeia* are efficiently updated. Any shortcoming identified in a national or regional pharmacopoeia should, of course, immediately be brought to the attention of the relevant authority.

## 2.7 International chemical reference substances

### 2.7.1 Reports from the WHO Collaborating Centre

Reports from the WHO Collaborating Centre for Chemical Reference Substances were reviewed by the Committee.<sup>1</sup>

### 2.7.2 Establishment of reference substances

During 1983, 10 new International Chemical Reference Substances were established and a further 5 replacement batches were introduced (Annex 3). The collection of materials now held by the Centre comprises 104 International Chemical Reference Substances and 13 Melting Point Reference Substances (Annex 3). The establishment of 22 further International Chemical Reference Substances to support specifications already published in *The international pharmacopoeia* and replacement batches for 5 existing reference substances will be required shortly. Work on about a dozen of these new reference substances is scheduled for completion by the end of 1983 but, with the resources at present available, the remaining substances required cannot be provided before 1985.

### 2.7.3 National or regional reference substances

In its twenty-eighth report (5) the Committee provided revised general guidelines to national and other authorities intending to establish, maintain, and distribute chemical reference substances. Within this context the WHO Collaborating Centre has offered, through the provision of consultancy services and training facilities, substantial assistance to organizations planning to establish collections of national or regional reference substances for use as working standards in quality control. Although the capacity of the Centre to provide such support is limited, it contributes in important measure to the harmonization of standards through the authentication of reference substances in different parts of the world.

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<sup>1</sup> WHO Collaborating Centre for Chemical Reference Substances. *Report on the work in 1981* (unpublished document WHO/PHARM/82.509); *Report on the work in 1982* (unpublished document WHO/PHARM/83.510).

#### 2.7.4 Future considerations

The Committee noted with appreciation the considerable contribution, both in terms of resources and finance, that has been made over many years by the National Corporation of Swedish Pharmacies to sustain the WHO Collaborating Centre for Chemical Reference Substances.

The cost of processing, evaluating, and distributing International Chemical Reference Substances has risen over the years to a level that threatens to jeopardize the future of the service. Consideration must consequently be directed to the feasibility of reducing the deficit of the WHO Collaborating Centre by:

(a) Favouring inclusion in *The international pharmacopoeia* of methods that do not involve the use of reference substances (see, for example, section 2.8 of this report relating to the use of infrared reference spectra).

(b) Reducing the amount of work undertaken to establish each reference substance. In advocating such a reduction, however, cognizance must be taken of the fact that International Chemical Reference Substances are frequently required for uses other than those foreseen in *The international pharmacopoeia*, e.g., for calibration of national or regional reference substances.

(c) Increasing standard charges for reference substances and reducing the extent to which they are distributed free of charge.

(d) Encouraging the institution in other regions of collaborating centres for the establishment and distribution of reference substances.

#### 2.8 Infrared reference spectra for pharmaceutical substances

The number of International Chemical Reference Substances that need to be established to support the monographs in *The international pharmacopoeia* grows proportionally with the preparation of new monographs. In about half these instances, reference substances are required solely for infrared identity tests. If infrared reference spectra were used instead for this purpose the demand for new reference materials would be correspondingly reduced.

The feasibility of replacing International Chemical Reference Substances by infrared reference spectra has accordingly been investigated. A collaborative study involving nine laboratories from

diverse regions was organized. This is described in detail in Annex 4. The results of the study indicated that each of the laboratories would have successfully verified the identity of a series of test substances by this means.

It is thus evident that, provided due care is taken in the preparation of samples and in the operation and maintenance of the spectrophotometer, the validity of employing infrared reference spectra to verify the identity of a drug substance is beyond doubt. It has to be conceded, however, that in another study in which a larger number of laboratories provided spectra, the results in some cases revealed inadequacy in either the instrumentation or the technique used.

It is thus essential that guidance be provided for the preparation of infrared spectra in identity tests, particularly in regard to the following points:

(a) the polystyrene film used for calibration should be protected from excessive moisture and temperature to preserve its characteristics;

(b) the resolution of the instrument should be verified and should conform to specified limits;

(c) samples to be tested should be prepared in conformity with the recommendations given in volume 1 of *The international pharmacopoeia*.

The Committee consequently proposes that infrared reference spectra be made available to replace International Chemical Reference Substances for infrared identity tests. Concordance between a reference spectrum and the spectrum provided by a sample under examination should be accepted as indicating compliance with the identity test.

Authentication of such spectra must be dependent upon evidence that they have been produced from materials complying with monograph requirements and that they have been approved by a review panel of specialists and, if possible, also by major manufacturers of the substance.

Initially an inventory of potential sources of such spectra will be compiled. It may be possible simply to refer to spectra already published either by governmental or private agencies provided it is ascertained that each spectrum meets the criteria referred to in Annex 4 and that full details of the pretreatment of the sample are provided.

If this approach is not feasible, WHO will investigate the possibility of producing and distributing spectra in collaboration with selected laboratories. It may be that tracings of infrared spectra could be generated on computerized instruments and supplied on request to national quality control laboratories.

### **2.9 Stability studies**

Results of a series of accelerated stability studies commissioned by WHO on about 300 long-established and widely-used pharmaceutical substances are detailed in two unpublished documents.<sup>1</sup> These have been issued in limited numbers on a consultative basis prior to publication. The results accord well with a series of prolonged stability tests undertaken by the WHO Collaborating Centre for Chemical Reference Substances under simulated tropical conditions of temperature and humidity.

## **3. BASIC TESTS**

The role and the limitations of basic tests were discussed in the Committee's twenty-eighth report (5). Considerable efforts have been made by various laboratories and individuals to develop and verify basic (or simplified) tests for some 250 substances. The guidelines applied to this work are given in Annex 6. Analytical laboratories, particularly in developing countries, that are willing to participate in the verification programme, are invited to contact WHO.

As stated in the twenty-eighth report (p. 12), "Basic tests are not, in any circumstances, intended to replace the requirements of pharmacopoeial monographs. The latter give an assurance of quality whereas basic tests merely confirm the identity".

## **4. TRAINING PROGRAMME IN DRUG ANALYSIS**

The establishment and development of pharmaceutical manufacturing facilities and of national quality control laboratories

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<sup>1</sup> PESEZ, M. *Studies on the stability of chemical substances for pharmaceutical use and on simple methods for detecting degradation*. Unpublished document WHO/PHARM/79.495; PESEZ, M. *Stability of pharmaceutical substances and simple methods of detecting their degradation*. Unpublished document WHO/PHARM/81.507.

in developing countries calls for the institution of relevant training programmes for technical personnel. In particular, there is an evident need for group training of recent science and pharmacy graduates embarking upon a career in this field, and for on-site individual training at more advanced level. Training of the latter type is already provided to individuals employed in national quality control laboratories through a scheme operated under the aegis of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).<sup>1</sup>

#### 4.1 Group training

Ideally, all graduate personnel should undergo a six-month period of preparatory training in practical and theoretical aspects of drug analysis. Emphasis should be on the practical approach, although some provisions should be made for discussion of the theoretical basis of the work, and the experimental programme should be developed having regard to:

- the structure and organization of the model laboratories described in Annex 1;
- common practical problems encountered in the analysis of pharmaceutical products;
- the importance of selecting and validating appropriate analytical methods and of evaluating all results.

Following an introductory course lasting about 1 week, in which the general principles of drug quality control and analysis are presented, including an appreciation of their relevance to procurement and distribution, separate courses should be offered in chemical, microbiological, and biological control. It is important, however, that a trainee in one of these disciplines should have a general appreciation of the other aspects of control. A clear perception must be gained of all the duties and responsibilities of an analyst and of the need to institute good laboratory practice in the interests of both efficiency and safety.

Basic training in microbiological control should lay particular emphasis upon sterility testing, microbiological spoilage testing, and

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<sup>1</sup> *Places of training in drug quality control offered by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA)*. Unpublished document WHO/PHARM/82.3/Rev. 1.

potency tests for antibiotics. Guidance is also required on the preparation and monitoring of culture media from locally available materials.

An introduction to biological control should be directed to pyrogen testing and other specific safety tests. Since the testing of biological products, including vaccines, blood products, and hormones, is usually undertaken in specialized institutions, this work falls outside the scope of a general introductory course.

WHO will identify possible centres for such training and also explore the possibility of organizing training for laboratory managers and technicians.

#### **4.2 Individual training**

Since the inception of the IFPMA training scheme in 1978, 26 analysts from national drug quality control laboratories in developing countries have been offered training in the quality control laboratories of pharmaceutical companies. This collaborative programme will now be extended beyond the initial pilot phase.

The Committee also acknowledged the support offered by the World Federation of Proprietary Medicines Manufacturers in organizing training in good manufacturing practices. It also stressed the need for facilities in laboratory management training. Considerable advantage could also accrue from linking the training now offered under the IFPMA scheme with attachments to governmental drug control laboratories and hospital pharmacies in the same countries. WHO was requested to explore these possibilities.

### **5. COLLABORATION WITH NONGOVERNMENTAL ORGANIZATIONS**

The Committee noted that the IFPMA, in addition to organizing training in quality control (see section 4), will seek to extend collaboration within the industry over the supply of samples of pharmaceutical substances for establishing international and regional chemical reference substances, which a number of companies have generously supplied on request for many years.

The Committee acknowledged the valuable cooperation offered by the International Pharmaceutical Federation (FIP) and particularly the sections concerned with official control laboratories and industrial pharmacists, in which pharmacopoeial standards and other aspects of regulatory control are prime foci of interest. The preparation of a manual for developing countries on *Management of drug purchasing, storage and distribution*, an offer to provide advice on pharmaceutical technology through WHO to institutions in developing countries, and the organization of workshops and fora devoted to problems arising in these countries, were cited as activities of direct relevance to the work of the Committee. It was suggested that, to encourage the participation of pharmacists from developing countries, occasional meetings might be organized in these areas.

## 6. CERTIFICATION SCHEME ON THE QUALITY OF PRODUCTS MOVING IN INTERNATIONAL COMMERCE<sup>1</sup>

A total of 106 countries now formally participate in this scheme, which is currently under evaluation. A questionnaire was circulated to all Member States through the WHO Regional Offices in 1983, and national responses have been followed up by consultants who have visited representative countries in various WHO regions. The final analyses of the responses to the questionnaire and the reports of the missions will form the basis of a report to be discussed at the Third International Conference of Drug Regulatory Authorities to be held in Stockholm in June 1984.

### REFERENCES

1. WHO Official Records, No. 226, 1975, p. 35 and Annex 12, p. 88 (regularly revised and reissued as PHARM/82.4).
2. WHO Technical Report Series, No. 645, 1980 (Twenty-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations).
3. WHO Technical Report Series, No. 685, 1983 (*The use of essential drugs*: report of a WHO Expert Committee).

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<sup>1</sup> Complete information is available in *Certification scheme on the quality of pharmaceutical products moving in international commerce*. Unpublished WHO document PHARM/82.4 Rev. 1.

4. *The international pharmacopoeia*, 3rd ed. Vol. 1. *General methods of analysis*, Geneva, World Health Organization, 1979. Vol. 2. *Quality specifications*, Geneva, World Health Organization, 1981.
5. WHO Technical Report Series, No. 681, 1982 (*WHO Expert Committee on Specifications for Pharmaceutical Preparations*: twenty-eighth report).

## ACKNOWLEDGEMENTS

The Committee acknowledges the special contributions made to its deliberations by the following staff members: Dr S. Kliouev, Senior Pharmaceutical Officer, Pharmaceuticals; Miss M. Schmid, Technical Assistant, Pharmaceuticals; Dr M.J. Vernengo, Project Manager, WHO/PAHO Drug Quality Project, São Paulo, Brazil.

The Committee also extends its thanks to the following persons for the valuable assistance they have given: Professor H.Y. Aboul-Enein, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; Professor A.S. Arambulo, College of Pharmacy, University of Illinois, Chicago, IL, USA; Dr T.D. Arias, Department of Investigation and Education, University of Panama, Panama, Republic of Panama; Dr I. Bayer, WHO Collaborating Centre for Drug Information and Quality Assurance, Budapest, Hungary; Professor A.H. Beckett, Chelsea College, University of London, London, England; Dr H.R. Bolliger, Hoffmann-La Roche Ltd., Basle, Switzerland; Professor J. Braun, Faculty of Pharmacy, University of Montreal, Montreal, Canada; Dr G.P. Carr, British Pharmacopoeia Commission Laboratory, Stanmore, England; Dr L. Cavatorta, Pierrel Ltd., Milan, Italy; Mr Chen Chang-lin, Commission of the Chinese Pharmacopoeia, Temple of Heaven, Beijing, China; Professor N.H. Choulis, Department of Pharmacy, University of Athens, Athens, Greece; Professor E. Cingolani, Italian Pharmacopoeia Commission, Rome, Italy; Professor Y. Cohen, Radioelements Department, Atomic Energy Commission, Gif-sur-Yvette, France; Dr D. Cook, Drug Research Laboratories, Health Protection Branch, Ottawa, Canada; Dr J. Cooper, Academy of Pharmaceutical Sciences, Belvedere, CA, USA; Dr L.F. Dodson, National Biological Standards Laboratory, Canberra, Australia; Dr M. El Fekih, Mutuelleville, Tunis, Tunisia; Professor J. Elis, State Institute for the Control of Drugs, Prague, Czechoslovakia; Dr K. Florey, The Squibb Institute for Medical Research, New Brunswick, NJ, USA; Dr D. Ganderton, Imperial Chemical Industries, Macclesfield, England; Professor H. Garcia Madrid, Department of Pharmacological Sciences, University of Chile, Santiago, Chile; Dr A.T. Gayot, Faculty of Pharmacy, Lille, France; Dr S. Görög, Chemical Works G. Richter Ltd., Budapest, Hungary; Professor F. Giral, Department of Pharmaceutical Chemistry and Natural Products, National University of Mexico, Mexico D.F., Mexico; Dr S.S. Gothoskar, Directorate General of Health Services, New Delhi, India; Dr A. Häussler, Hoechst Ltd., Frankfurt, Federal Republic of Germany; Mr W. Hewitt, Cheltenham, England; Dr F. Hippenmeier, Cantonal Laboratory of Pharmacy, Zurich, Switzerland; Dr T. Inoue, The Society of the Japanese Pharmacopoeia, Tokyo, Japan; Professor P. Ionesco-Stoian, Academy of Medical Sciences, Bucarest, Romania; Mr D. Jäkel, Ciba-Geigy Ltd., Basle, Switzerland; Miss S. Johansson, WHO Collaborating Centre for Chemical Reference Substances, Solna, Sweden; Dr F. Johnson-Romuald, Ministry of Public Health, Lomé, Togo; Dr T.M. Jones, The Wellcome Foundation Ltd., Dartford, England; Dr J. Kawamura, Division of Biological Chemistry and Reference Standards, National Institute of Hygienic Sciences, Tokyo, Japan; Dr R.A. Khan, London,

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## Annex 1

### NATIONAL LABORATORIES FOR DRUG QUALITY SURVEILLANCE AND CONTROL

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## 1. INTRODUCTION

The capacity of a drug regulatory authority to undertake quality surveillance is directly related to the operational capability of the associated national quality control laboratories. The results of laboratory assessment of samples of marketed drugs permit the regulatory authority to evaluate the actual quality of products used in the country and to identify the problem areas. When no independent analytical service is available to the regulatory authority, judgements on the quality of drugs must be based largely on data supplied by manufacturers or importers, which are inherently difficult to challenge.

The importance of a drug control laboratory to the implementation of surveillance as an element of quality assurance in pharmaceutical supply systems has been stressed in Annex 1 of the twenty-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.<sup>1</sup> Developing countries are particularly vulnerable to the supply of substandard drugs and, where no testing facilities exist, such problems can be particularly acute. This annex therefore examines the principles that should determine the structure and management of a national drug quality control laboratory where no such facility yet exists.

National authorities have the option of establishing either a central laboratory or a number of smaller laboratories dispersed throughout the country. Even the existence of a single small laboratory, when it is concerned with priority issues and perceptively managed, can offer a deterrent against unscrupulous or negligent manufacturing and trading practices. It is also evident that standards of local manufacturers will tend to rise whenever the possibility of an independent assessment of the quality of their products exists.

The laboratory would at least have the potential to detect products, both raw materials and dosage forms, that have been mislabelled, and to detect adulterated and spurious products. Its capacity to undertake full analyses of products to check their conformity with labelled specifications would be severely limited. Clear priorities would therefore need to be set to ensure that attention is concentrated upon products that are of prime

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<sup>1</sup> WHO Technical Report Series, No. 645, 1980.

importance to public health programmes, or that are potentially dangerous, unstable, or unusually expensive.

The advice contained in the following paragraphs applies to the organization and staffing of two model laboratories, one of medium size and the other providing minimum facilities for efficient work. The latter is designated as a first-stage laboratory for drug surveillance. Although provision is made for some types of biological testing by the laboratories described here, they are not equipped for the testing of sera and vaccines. No consideration is given to larger-scale drug control laboratories, having regard to the limited resources available for such purposes in most developing countries.

Matters concerning the management and operation of drug control laboratories do not fall within the scope of these recommendations; these aspects will be the subject of a separate WHO document.

## **2. FIRST-STAGE LABORATORY FOR DRUG SURVEILLANCE**

This small laboratory has a floor space of 60 m<sup>2</sup>. It is staffed by one analyst, 2 technicians, and 1–2 housekeeping staff.

Such a laboratory cannot be effectively maintained as an independent unit. It should be incorporated within another governmental laboratory or be sited within a large regional hospital. This provides access to existing technical and library facilities, utilities, and supply arrangements. It is important, none the less, that the manager should remain organizationally independent in the execution of his duties, and that the laboratory should be accorded an independent budget.

It is estimated that such a laboratory could undertake annually 200–300 full analyses (samples fully tested and evaluated in accordance with quality specifications) or a greater number of partial analyses.

The analyst, who should have a proven ability to work independently, should be university trained in pharmacy or chemistry and should have received practical training in an established drug quality control laboratory for 6 months to two years, as determined by background experience. An institutional

training for technicians is desirable in addition to in-service training in the laboratory.

The laboratory premises should be provided with basic utilities (water, drainage, and electricity) and equipped with a hot-water source, a distilled-water still, and a propane gas tank, if a piped gas supply is not available. If the laboratory is to be located in a newly erected building it is best constructed as a basic module that may be subsequently extended.

The laboratory furniture, which should be arranged to provide an efficient but uncongested working space, must include: one double chemical bench with two lateral sinks located in the centre of the module, a fume hood, one laboratory bench for instruments, a table for balances, one storage cabinet for solvents, one refrigerator (with freezer compartment), wall shelves, and writing desk. The bench for instruments and the table for balances are positioned in a separate part of the module to protect the instruments from corrosion.

Important items of laboratory equipment are given in Table 1. No listing of reagents or glassware is provided as such lists are best compiled within the laboratory. Provision should always be made for an adequate reserve of glassware and sundry items. This is of particular importance where difficulties in delivery are anticipated.

Table 1. First-stage laboratory for drug surveillance

<i>Equipment and major instruments</i>	No.		
Analytical balance (four place, mechanical)	1	Disintegration test equipment	1
Spectrophotometer (UV/visible, single-beam; manual)	1	Microscope	1
pH-meter (with electrodes)	1	Refrigerator (with freezer compartment)	1
Karl-Fischer titrator	1	Micrometer calipers	1
Melting-point apparatus	1		
Polarimeter (manual)	1	<i>Optional items</i>	
Drying oven	1	Flame photometer	1
Vacuum oven	1	Osmometer	1
Vacuum pump	1	Vortex mixer	1
Centrifuge (table-top)	1	Constant temperature water-bath	1
Hot plate with stirrer	3	Ultrasonic cleaner	1
Equipment for thin-layer chromatography including:		Refractometer	1
- spreader	1	Shaker (wrist-action)	1
- spotting equipment	1	Oxygen flask combustion apparatus	1
- developing chambers	6		
- spraying bottles	6		
- UV viewing lamp	1		

### **3. MEDIUM-SIZE DRUG CONTROL LABORATORY**

#### **3.1 Capability**

This laboratory is designed to deal with some 1500 full analyses per year and is equipped to provide for almost all types of test for drug identity and purity, all assays for content and strength based on chemical, instrumental, and microbiological techniques, and various performance tests for dosage forms.

The laboratory has several discrete components, including a chemical unit, an instrumental unit, a microbiological unit, a unit for biological safety tests (e.g., pyrogen testing), a pharmacognostic unit and, if appropriate, a special dosage-form unit. It should also have a library of reference books, manuals, and professional and scientific journals.

#### **3.2 Premises**

A floor space of 300–400 m<sup>2</sup> is required. All laboratory rooms should be supplied with running water and drainage, electrical power, and gas (either centrally supplied or from a gas tank). Climatic conditions will determine the need for air-conditioning and heating systems. The supply of water should be of adequate pressure for the use of vacuum aspirators (at least 19 kPa or 20 N/cm<sup>2</sup> are needed), otherwise suitable vacuum pumps should be installed. An arrangement to recirculate water used by vacuum aspirators through a collection tank may considerably reduce total water needs and should be considered if the water supply is scarce or irregular. A sewage treatment installation should also be provided (e.g., a lime pit to neutralize acidic effluents). The building should be constructed of fire-resistant material and the layout of the modules and connecting corridors should be determined not only by working efficiency but also by safety considerations, particularly in areas where inflammable liquids or compressed gases are used or stored. If large quantities of inflammable reagents are to be stored, the space should be planned and constructed in accordance with local fire regulations.

Each unit should be provided with rooms equipped for its specific requirements, including hooded benches in chemical rooms; ample

electrical outlets in physicochemical rooms and voltage-stabilizing equipment if the local power supply is variable; movement-damping tables in balance rooms; laminar airflow equipment in microbiological rooms. All rooms should be provided with storage cabinets for reagents, glassware, and samples, wall shelving, and writing desks.

Control of temperature and humidity of at least a part of the laboratory area is imperative in tropical regions. In particular, the room for chromatographic work (primarily thin-layer chromatography) should be thermostatically controlled and in all cases protected from draughts and direct sunlight. Rooms equipped with hoods and extractor fans should receive an inflow of dry, cool air and additional dehumidifiers are required in storage areas for reference materials and samples.

Rabbits used for pyrogen testing should be kept in a room apart from other areas of the laboratory. A separate unit should be provided if other experiments on animals are contemplated. Both the animal house and the animal experimentation rooms should be thermostatically controlled within  $\pm 2^{\circ}\text{C}$ . In warmer climates the temperature is usually maintained within the range 23–25°C.

Advice on technical facilities required for microbiological testing is provided in the twenty-second report of the WHO Expert Committee on Biological Standardization.<sup>1</sup>

### 3.3 Staff

The staffing complement comprises 14–18 persons, including the head of the laboratory, 4–5 analysts, 6–8 laboratory technicians, and 2–4 supporting and housekeeping staff. The ratio of analysts to laboratory technicians must be relatively high in a laboratory carrying out analyses on a wide range of pharmaceutical products. The ratio may be reduced in laboratories involved in repetitive testing of batches of a limited number of products.

The head of the laboratory should be a graduate in pharmacy or chemistry, preferably with a postgraduate degree in pharmaceutical analysis or related subjects and with broad practical experience in the many facets of drug quality assessment. The analysts should be

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<sup>1</sup> WHO Technical Report Series, No. 444, 1982.

graduates in pharmacy, analytical chemistry, biochemistry, or microbiology, as appropriate to their assigned responsibilities. An institutional training for the technicians is desirable, otherwise provision must be made for in-service training in the laboratory. High ethical standards are mandatory for the head of the laboratory and the analysts.

### 3.4 Equipment

The general laboratory equipment, together with items required in the chemical unit, are listed in Table 2. Water demineralizers and distillation stills are always needed, but their number or capacity can be reduced if a reliable supply of demineralized or distilled water is available from an outside source.

Major items of equipment required for the instrumental unit and for testing of dosage forms, as well as the equipment required for the microbiological unit are also listed in Table 2. Advice on the required performance of many of these instruments is included in *The international pharmacopoeia*.<sup>1</sup>

It is essential to ensure, before major items of equipment are purchased, that facilities are available for their proper maintenance and repair, preferably by representatives of the manufacturer. Electrical equipment must be compatible with the existing frequency and line voltage. Standard sets of replacement parts required for running repairs, containing such items as gaskets and spare bulbs, should always be retained in stock. Certain types of equipment, including gas-liquid and high-pressure liquid chromatographs and atomic absorption spectrophotometers, require a constant supply of special solvents, reagents, and compressed gases of high purity. It is essential that the availability of these is also ascertained before purchase. It can be helpful in selecting apparatus to seek information on the performance of instruments from other laboratories, particularly within the same region.

Requirements for glassware and general laboratory apparatus will vary from case to case and cannot be specified in general terms. Provision must be made for an adequate reserve. Lists of

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<sup>1</sup> *The international pharmacopoeia*. 3rd ed. Volume 1. *General methods of analysis*. Geneva, World Health Organization, 1979. Volume 2. *Quality specifications*. Geneva, World Health Organization, 1981.

Table 2. Medium-size control laboratory

<i>General laboratory equipment</i>	No.	<i>Major instruments (continued)</i>	No.
Microbalance (five-place)	1	Penetrometer	1
Analytical balance (four-place)	2	IR hydraulic pellet press with dies (15 tonf/in <sup>2</sup> pressure $\approx 23 \times 10^7$ Pa)	1
Laboratory balance (top-loading)	1-2	Agate mortar with pestle	1
Refrigerator (with freezer compartment)	2-3	Karl-Fischer titrator	1
Water distillation still (10 litres/hour)	1	Oxygen flask combustion apparatus	1
Water deionizing equipment (10 litres/hour)	1		
Drying oven	2-3		
Muffle furnace	1	<i>Optional items</i>	
Vacuum oven	1	Ice machine	1
Heating plates with magnetic stirrers	3-4	Solvent recovery apparatus	1
Vacuum rotary evaporator	1-2	Flame photometer or atomic absorption spectrophotometer	1
Water-bath (electrical)	2-3	Osmometer	1
Automatic titrimeter	1	Vibrospatula	1
Shaker (wrist-action)	1	High-pressure liquid chromatograph	1
Micro-Kjeldahl equipment	1	Densitometer for TLC plates	1
Equipment for thin-layer chromatography including		Fluorometer (filter)	1
- spreader	1	Hardness tester	1
- spotting equipment	1	Friability tester	1
- developing chambers	10	Viscosimeter	1
- spraying bottles	6		
- UV viewing lamps	3		
Laboratory centrifuge (floor model)	1		
Ultrasonic cleaner	2	<i>Equipment for microbiology unit</i>	
Vortex mixers	2	Autoclaves	2
Heating mantles for flasks (assorted sizes)	6	Microscopes (bacteriological)	2
Variable transformers	5	Incubators*	2-3
Vacuum pump (rotary, oil)	2	Centrifuge with refrigeration	1
Micrometer calipers	1	Membrane filter assembly for sterility tests	1
Glove box	1	Colony counter with magnifier	1
Sieves (set)	2	Laminar flow bench	1
Microscope	1-2	Hot-air sterilizer	1
		Spectrophotometer, visible range (simple model)	1
<i>Major instruments</i>		Nephelometer (+ turbidimeter)	1
IR spectrophotometer (recording, grating)	1	Refrigerators	2
UV/visible recording spectrophotometer	1	Deep freezer	1
UV/visible spectrophotometer	1	Large-plate microbiological assay equipment, including zone reader and recorder	1 set
Gas chromatograph	1	pH-meter	1
Polarimeter (manual)	1	Cleaning machines for glassware, especially one for cleaning pipettes	2
Refractometer	1	Water-baths (thermostatically controlled)	2
pH-meters (with electrodes)	2		
Melting-point apparatus (electrically heated)	1		
Disintegration test equipment	1		
Dissolution test equipment (for 6 tablets/capsules)	1		

\*Cooling incubators in countries with tropical climates.

reagents to be held in stock are included in *The international pharmacopoeia*.

Additional equipment will be required if the basic range of tests is extended. Thus, pyrogen testing necessitates provision of animal housing, restraining harnesses or boxes, and a temperature-recording device with probes. An osmometer is required for testing large-volume parenteral preparations.

#### 4. SCOPE OF ACTIVITY

The principal responsibilities are as follows:

—to establish, by testing, whether a given sample of a drug, either locally manufactured or imported, conforms to required specifications and whether packaging is adequate;

—to examine pharmaceutical products suspected to be of questionable efficacy or safety, and to demonstrate and document any evidence of deterioration, contamination, or adulteration;

—to check the stability of products under local conditions of storage.

Other responsibilities that may devolve upon the laboratory include:

—evaluating data supplied by manufacturers concerning product performance;

—determining whether the product label provides appropriate and clear instructions for use;

—advising on planned purchases of drugs within the public sector.

These additional activities require qualified staff and library facilities. However, since they are not directly dependent on the use of laboratory facilities, the necessary resources have not been taken into consideration within this annex.

In developed countries, drug-licensing regulations require an independent examination of data supplied by the manufacturer in support of an application for registration of a product. The required pharmaceutical data are detailed in Annex 5 to the twenty-fifth report of the WHO Expert Committee on Specifications for

Pharmaceutical Preparations.<sup>1</sup> When resources are available for such work, review and verification of these data by critical examination of pertinent quality specifications may be included among the responsibilities of a large drug control laboratory or it may be undertaken in a separate laboratory associated with the regulatory authority. No provision for these activities has been made in the laboratories described in sections 2 and 3.

## **5. FACTORS INFLUENCING THE SIZE AND LOCATION OF A LABORATORY**

Many considerations determine the location, size, and organization of a national control laboratory. They include: financial resources; the drug control requirements of the national regulatory authority; the extent of drug usage within the country; and the number of different sources from which products are purchased.

If a country has a decentralized national administrative structure or if communications are poor, it may be necessary to establish provincial or peripheral laboratories.

Careful consideration must also be accorded to organizational and professional links between the control laboratory and other public health services, including food control laboratories, microbiological laboratories, hospital or regional clinical laboratories, and university departments of medicine or pharmacy.

Although it is practicable to institute and run a medium-size control laboratory apart from other laboratory services, economies can be effected by siting it in a complex together with other institutions. This enables the laboratory to retain independence of operation, while sharing common supporting services (e.g., supply units, maintenance crews, and repair shops). It also offers the possibility of using specialized facilities in adjacent laboratories (e.g., bacteriological laboratories for sterility testing) instead of duplicating the same facilities within the drug control laboratory.

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<sup>1</sup> WHO Technical Report Series, No. 567, 1975.

## **6. IMPLEMENTATION OF CONTROL LABORATORY PROJECTS**

### **6.1 Feasibility study**

Before any definitive steps are taken to establish a national laboratory service for drug control, a feasibility study must be put in hand to assess, within the context of prevailing needs and legal and administrative provisions, the precise functions it will serve, the scale of operation, and the projected costs. Provision must be made in the costing for: land and/or buildings, services, furnishings, equipment, consultancy fees, training of staff, and routine maintenance and operational costs. The necessity or practicability of phasing the development of the service should also be examined.

### **6.2 Phasing of development**

The rate of development of any laboratory service is commonly limited by the availability of qualified and experienced personnel and the possibilities for further training. New techniques should never be introduced into routine testing programmes until a high standard of performance is assured. Initially, it is prudent to concentrate on the development of chemical and physical techniques of analysis and testing, and to defer the introduction of microbiological and biological techniques to a later stage.

### **6.3 Programme support**

The calibre of the professional personnel is the ultimate determinant of the standard and value of the laboratory service; they must have a high degree of technical competence, motivation, critical ability, and professional integrity. Inculcation of these qualities can be promoted during in-service training in established laboratories and by engaging consultants of repute in newly established national laboratories.

Training facilities for specialized analytical techniques should be made available in countries where they are already established. Recognizing the great need and the limited resources available within the least developed countries, it is to be hoped that relevant assistance may be forthcoming through bilateral and multilateral aid programmes.

## QUALITY REQUIREMENTS FOR PHARMACEUTICAL AIDS

### 1. General

Drug formulation is directed to ensuring that a given dosage form is acceptably stable and palatable in the case of orally administered preparations, and that it releases the active ingredients in a manner appropriate to the intended route of administration. The technology involved in this development work and in subsequent manufacturing procedures can be complex. It involves the use of various substances (or pharmaceutical aids) that do not contribute directly to the pharmacological action of the product. These substances are categorized according to their function. Some of them, including filling, binding, sweetening, flavouring and colouring agents, and preservatives, are contained in the dosage form itself in demonstrable amounts. Collective terms, such as excipients, added substances, auxiliary substances, and pharmaceutical adjuvants have been applied, sometimes selectively, to such substances. It is proposed that the term pharmaceutical aids, with its broader connotation, should embrace all the substances that come into consideration.

It is misconceived to regard these substances as inert, either chemically or pharmacologically. They must be chosen with care to avoid unintended interactions with each other or with the active ingredients. Such interactions can result from faulty formulation by inexperienced manufacturers. All manufacturers of dosage forms should have their practices constantly under review and keep themselves informed of new developments and newly introduced materials in this highly specialized field.

### 2. Aspects of Quality Control of Pharmaceutical Aids

Pharmaceutical aids comprise a broad range of substances some of which are synthetic while others are naturally occurring. Some are well-defined, whereas others are materials of complex composition, such as mixtures of homologues. As a consequence, the analytical techniques needed to verify the identity of these substances, to determine their purity and, when required, to determine their

suitability for a specific purpose are widely varied and may differ in many respects from those used for active materials.

As with active materials,<sup>1</sup> quality specifications for individual pharmaceutical aids identify the material and define standards for its purity. They may, as appropriate, additionally serve to define any special characteristics relevant to its use in the formulation process.

In setting specifications for these substances, it must be appreciated that many of them have other uses and applications, and that most are manufactured or processed outside the pharmaceutical industry. Technical grades may therefore exist that are unsuited to applications in pharmaceutical formulation. Purity limits (and other characteristics) should be designed to exclude the use of such substances. It is also important that these purity requirements have regard to the origin of the material and subsequent production processes (for example, residual monomers are liable to occur in polymeric materials). In the case of substances of complex composition, quantitative limits included in the specification should permit the use of the whole range of suitable materials that are present on the market.

However, purity requirements can vary according to the intended use of a substance. Thus, more stringent microbiological standards are required for parenteral than for oral preparations. When a material is used for two such manifestly different purposes, or when it is derived from two or more different source materials, the main monograph should be supplemented with additional requirements for specific grades or specific source materials as needed. Supplementary specifications may also be required, on occasion, for substances used both as active materials and as pharmaceutical aids, (e.g., ascorbic acid, citric acid, glucose, mannitol, sodium hydrogen carbonate, sodium chloride, sodium citrate). In other cases, a reference to a monograph in *The international pharmacopoeia* will suffice.

Some important physical properties of pharmaceutical aids, such as particle size distribution and surface area, that determine the technological behaviour of the substance have to be considered in relation to each specific intended use. A pharmacopoeial monograph is not intended to define such technological characteristics, which must be studied in specific performance tests undertaken during the development of the dosage form.

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<sup>1</sup> WHO Technical Report Series, No. 614, 1977 (*WHO Expert Committee on Specifications for Pharmaceutical Preparations*: twenty-sixth report), Annex 1.

### Annex 3

## INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

### 1. Establishment of new reference substances

The following new International Chemical Reference Substances have been established:

amitriptyline hydrochloride  
caffeine  
2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid  
chlorphenamine hydrogen maleate  
diazoxide  
diethylcarbamazine dihydrogen citrate  
fluphenazine decanoate dihydrochloride  
lidocaine  
lidocaine hydrochloride  
pyridostigmine bromide

### 2. Replacement of current reference substances

Replacement batches of the following International Chemical Reference Substances have been introduced:

etacrynic acid  
lanatoside C  
oxacillin sodium  
retinol acetate (vitamin A acetate)  
riboflavin

### 3. List of International Chemical Reference Substances, January 1983

International Chemical Reference Substances are established upon 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*.

International Chemical Reference Substances may also be used in tests and assays not described in *The international pharmacopoeia*.

However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed these substances to be used.

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

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

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 of the Centre and may be obtained on request.

Orders for the International Chemical Reference Substances should be sent to WHO Collaborating Centre for Chemical Reference Substances, Apoteksbolaget AB, Centrallaboratoriet, P.O. Box 3045, S-171 03 Solna, Sweden, (Telex: 115 53)

The reference substances available and the packages in which they are supplied are shown in the following list:

<i>Reference substance</i>	<i>Package size</i>
aceclidine salicylate	100 mg
<i>p</i> -acetamidobenzalazine	100 mg
allopurinol	100 mg
3-aminopyrazole-4-carboxamide hemisulfate	100 mg
amitriptyline hydrochloride	100 mg
ampicillin	200 mg
ampicillin sodium	200 mg
ampicillin trihydrate	200 mg
anhydrotetracycline hydrochloride	25 mg
azathioprine	100 mg
bendazol hydrochloride	100 mg

<i>Reference substance</i>	<i>Package size</i>
benzobarbital	100 mg
benzylamine sulfate	100 mg
benzylpenicillin potassium	200 mg
benzylpenicillin sodium	200 mg
betanidine sulfate	100 mg
bupivacaine hydrochloride	100 mg
caffeine	100 mg
carbenicillin sodium	200 mg
chloramphenicol	200 mg
chloramphenicol palmitate	1 g
chloramphenicol palmitate (polymorph A)	200 mg
5-chloro-2-methylaminobenzophenone	100 mg
2-(4-chloro-3-sulfamoylbenzoyl)benzoic acid	50 mg
chlorphenamine hydrogen maleate	100 mg
chlorpromazine hydrochloride	100 mg
cloxacillin sodium	200 mg
cortisone acetate	100 mg
desoxycortone acetate	100 mg
dexamethasone	100 mg
dexamethasone acetate	100 mg
diazepam	100 mg
diazoxide	100 mg
dicloxacillin sodium	200 mg
dicolinium iodide	100 mg
dicoumarol	100 mg
diethylcarbamazine dihydrogen citrate	100 mg
digitoxin	100 mg
digoxin	100 mg
<i>NN'</i> -di-(2,3-xylyl)anthranilamide	50 mg
4-epianhydrotetracycline hydrochloride	25 mg
4-epitetracycline ammonium salt	25 mg
ergometrine hydrogen maleate	50 mg
ergotamine tartrate	50 mg
estradiol benzoate	100 mg
estrone	100 mg
etacrynic acid	100 mg
ethambutol hydrochloride	100 mg
ethinylestradiol	100 mg

<i>Reference substance</i>	<i>Package size</i>
ethisterone	100 mg
ethosuximide	100 mg
etocarlide	100 mg
fluphenazine hydrochloride	100 mg
fluphenazine decanoate dihydrochloride	100 mg
fluphenazine enantate dihydrochloride	100 mg
folic acid	100 mg
furosemide	100 mg
griseofulvin	200 mg
haloperidol	100 mg
hydrochlorothiazide	100 mg
hydrocortisone	100 mg
hydrocortisone acetate	100 mg
(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine	25 mg
imipramine hydrochloride	100 mg
indometacin	100 mg
<i>o</i> -iodohippuric acid	100 mg
lanatoside C	100 mg
levodopa	100 mg
lidocaine	100 mg
lidocaine hydrochloride	100 mg
mefenamic acid	100 mg
melting point reference substances (set of 13 substances with melting temperatures ranging from +69 °C to +263 °C)	13 × 4 g
metazide	100 mg
methaqualone	100 mg
methyldopa	100 mg
methyltestosterone	100 mg
meticillin sodium	200 mg
nafcillin sodium	200 mg
nicotinamide	100 mg
nicotinic acid	100 mg
ouabain	100 mg
oxacillin sodium	200 mg
pheneticillin potassium	200 mg
phenoxymethylpenicillin	200 mg
phenoxymethylpenicillin calcium	200 mg

<i>Reference substance</i>	<i>Package size</i>
phenoxymethylpenicillin potassium	200 mg
phenytoin	100 mg
prednisolone	100 mg
prednisolone acetate	100 mg
prednisone	100 mg
prednisone acetate	100 mg
progesterone	100 mg
propicillin potassium	200 mg
pyridostigmine bromide	100 mg
riboflavin	250 mg
rose Bengal sodium	100 mg
sulfamethoxazole	100 mg
sulfamethoxypyridazine	100 mg
sulfanilamide	100 mg
testosterone propionate	100 mg
tetracycline hydrochloride	200 mg
thioacetazone	100 mg
tolbutamide	100 mg
tolnaftate	100 mg
trimethoprim	100 mg
trimethylguanidine sulfate	100 mg
tubocurarine chloride	100 mg
vitamin A acetate (solution)	5 capsules <sup>a</sup>
warfarin	100 mg

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<sup>a</sup> About 9 mg in 250 mg of oil per capsule.

## Annex 4

### COLLABORATIVE STUDY ON INFRARED REFERENCE SPECTRA FOR PHARMACEUTICAL SUBSTANCES

#### 1. General considerations

In several of its reports, the WHO Expert Committee on Specifications for Pharmaceutical Preparations has urged that, having regard to cost, analytical methods requiring the use of reference materials should be avoided as far as possible in *The international pharmacopoeia*.<sup>1</sup> The expense and difficulty of obtaining and distributing reference substances on a worldwide basis for use in tests of identity specified in *The international pharmacopoeia* makes it necessary to consider the replacement of reference substances, where appropriate, by reference spectra. Savings in costs of establishing and distributing reference substances and the provision of a reference standard that is not subject to deterioration would be of direct advantage to users.

These advantages must be weighed against new technical demands upon analysts; the need for standardization of methods, particularly in the preparation of samples; and the possibility that either polymorphism or differences in resolution and registration of spectrophotometers may influence the interpretation. None the less, experience in countries in which reference spectra are already in use for pharmacopoeial purposes has apparently been favourable.

It is evident that reference spectra can only partially reduce the need for chemical reference substances, which may be used in pharmacopoeial work for purposes other than the generation of infrared spectra. Ideally, chemical reference substances should remain available even when corresponding reference spectra have been introduced.

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<sup>1</sup> *The international pharmacopoeia*, 3rd ed., volume 1. *General methods of analysis*, Geneva, World Health Organization, 1979. Volume 2. *Quality specifications*, Geneva, World Health Organization, 1981.

## 2. Infrared reference spectra for use in conjunction with *The international pharmacopoeia*

In anticipation of the establishment of a collection of infrared reference spectra suitable for use in conjunction with *The international pharmacopoeia*, many of the monographs already provide for their optional use instead of International Chemical Reference Substances.

Various collections of infrared spectra already exist, some of which have been prepared specifically for pharmacopoeial work. An officially recognized WHO collection could thus be developed either *de novo* or by the adoption of existing collections subject to agreement.

Compilation of a new collection would require procurement of adequately authenticated substances and the generation of spectra according to standardized methods in one or more collaborating laboratories. Particular attention would need to be accorded to any problems that might result from polymorphism.

Highly purified substances are not usually required for this purpose, although the use of existing official reference substances is preferable. In every case, to increase the likelihood of detecting troublesome polymorphism, validation should be undertaken independently in several laboratories.

## 3. Organization of the collaborative study

A collaborative study to explore the practicability of employing reference spectra in a broad international context has recently been completed. Each participating laboratory<sup>a</sup> recorded the spectra of a

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<sup>a</sup> The following laboratories collaborated in the study:

1. Central Drugs Laboratory, Calcutta, India
2. Department of Scientific Services, Singapore
3. Institute of Drug Research and Control, Warsaw, Poland
4. Laboratory of the British Pharmacopoeia Commission, London, England
5. Laboratory of Drug Standards Division, United States Pharmacopoeia, Rockville, MD, USA
6. National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China
7. Squibb Institute for Medical Research, New Brunswick, NJ, USA
8. State Scientific Institute for the Specification and Control of Drugs, Moscow, USSR
9. WHO Collaborating Centre for Chemical Reference Substances, Solna, Sweden

polystyrene film and of three test substances, provided both as International Chemical Reference Substances and as locally available materials. The resulting spectra were then submitted to an international panel for review.

The substances selected were: hydrocortisone, benzylpenicillin potassium, and diazepam.

In each case, international chemical reference substances and locally available materials were examined.

Samples were prepared using potassium bromide discs and spectra were registered under the normal working conditions of each laboratory. Details were submitted of the method of preparation of the discs (e.g., weight of sample and of potassium bromide, any manipulation of the sample in a ball mill) and of the type, age, and condition of the spectrophotometer used.

#### 4. Results of the collaborative study

Samples of all three substances were prepared in potassium bromide discs using quantities ranging arbitrarily from 0.1 mg to 0.5 mg per 100 mg of potassium bromide. The spectra were recorded in the ranges  $4000\text{ cm}^{-1}$  to  $600\text{ cm}^{-1}$ ,  $4000\text{ cm}^{-1}$  to  $400\text{ cm}^{-1}$ , or  $4000\text{ cm}^{-1}$  to  $200\text{ cm}^{-1}$  on spectrophotometers of various types and models that had been in service for periods ranging up to five years. Most spectra were 51–71 cm in length and 15–25.5 cm in width, but one instrument produced tracings measuring  $28 \times 15$  cm. The scan time ranged from 6 to 13 minutes.

Spectra were compared by evaluating the number of resolved peaks between  $4000\text{ cm}^{-1}$  and  $600\text{ cm}^{-1}$ , the range within which all the instruments were operational. Within each set, the spectrum containing the greatest number of peaks was used as the point of reference. The position of the peaks could not be determined with precision because reference polystyrene peaks were not superimposed on the tracings. The values shown in Tables 2–4 are therefore presented in  $\text{cm}^{-1}$  without correction.

All laboratories would have successfully verified the identity of benzylpenicillin potassium and of diazepam and all but one would have verified the identity of hydrocortisone. This failure was attributed by the assessors to deficiencies in sample preparation rather than a failing inherent in the method. Detailed analyses are presented in Tables 1–4.

The greatest divergences occurred in the spectra of polystyrene films. This presumably results from surface deterioration and uptake of moisture. It was consequently proposed that the section of infrared spectrophotometry in volume 1 of *The international pharmacopoeia* be modified to:

(1) Provide additional details on the care of polystyrene films.

(2) Include a table listing the principal peaks of polystyrene film and prescribing a minimum resolution as in the *European Pharmacopoeia*.<sup>1</sup> This requires that the difference in percentage transmission between the minimum at  $2870\text{ cm}^{-1}$  and maximum at  $2851\text{ cm}^{-1}$  should be greater than 18, and that the difference between the minimum at  $1589\text{ cm}^{-1}$  and the maximum at  $1583\text{ cm}^{-1}$  should be greater than 12.

(3) Replace the existing requirement for concordance of *relative intensities* by a requirement for concordance of spectra.

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<sup>1</sup> Council of Europe. European Pharmacopoeia Commission. *European Pharmacopoeia*, 2nd ed. Ste-Ruffine, Maisonneuve, 1980, section V.6.18.

Table 1. Polystyrene film: verification of the wave number scale and resolution performance

Collaborating laboratory	Verification of the wave number scale (cm <sup>-1</sup> )										Resolution performance as difference in percentage transmission between		
	3027.1	2850.7	1944.0	1801.6	1601.4	1583.1	1154.3	1028.0	906.7	min. 2870	1589	max. 2851	1583
I	3027	2850	1945	1801	1601	1583	1154	1028	906	22	16	22	16
II	3025	2850	1944	1801	1601	1583	1154	1028	906	19	25	19	25
III	3019	2842	1940	1798	1558	1581	1150	1024	900	19	21	19	21
IV	3026	2850	1944	1802	1601	1583	1154	1028	904	22	18	22	18
V	3025	2848	1944	1800	1600	1582	1152	1026	904	22	14	22	14
VI	3020	2840	1930	1790	1592	1575	1150	1025	905	22	16	22	16
VII	3027	2850	1942	1802	1600	1582	1154	1028	906	23	18	23	18
VIII	3028	2849	1942	1805	1598	1580	1150	1024	900	17	23	17	23
IX	3025	2850	1945	1805	1601	1584	1155	1028	906	25	14	25	14

Table 2. Benzylpenicillin potassium

Peaks	Wave number in cm <sup>-1</sup>								
	I <sup>a</sup>	II	III	IV	V	VI	VII	VIII	IX
1	3370	3370	3362	3372	3370	—	3369	3370	3370
2	3082	3082	W	3378	3382	3378	3085	3085	3080
3	3029	3030	3022	3025	3025	3020	3029	3029	3029
4	2998	2998	2980	2995	2990	2980	2994	3000	—
5	2964	2960	2962	2965	2960	2955	2964	2960	2960
6	2920	2920	2920	2920	2916	2910	2918	2920	2920
7	2852	2850	W	W	2850	W	2850	W	2852
8	1775	1775	1774	1775	1775	1765	1775	1775	1775
9	1760	1755	1755	1755	1755	—	1756	—	1755
10	1720	W	—	W	W	W	W	—	W
11	1670	1670	1667	1670	1667	1660	1656	1670	1670
12	1612	1610	1610	1612	1610	1603	1610	1615	1612
13	1580	W	—	1585	1576	—	W	—	W
14	1492	1490	1490	1495	1490	1485	1491	1490	1492
15	1462	W	—	1462	—	—	1462	—	—
16	1455	1455	1450	1455	1455	1445	1452	—	1455
17	1415	—	—	W	W	—	W	—	—
18	1400	1415	1410	1415	1410	1408	1413	1400	W
19	1395	1395	1394	1395	1395	1390	1395	—	1395
20	1370	1370	1362	1358	1363	1360	1367	—	W
21	1335	1330	1330	1335	1330	1325	1332	1330	1335
22	1318	1315	1315	1318	1315	1310	1316	—	1318
23	1250	1250	1245	1250	1245	1245	1247	1245	1250
24	1215	1215	1210	1215	1210	1210	1214	1210	1215
25	1192	W	—	W	W	—	1192	—	W
26	1178	1180	1170	1175	1175	1170	1178	—	W
27	1153	1153	1150	1152	1153	1150	1153	1155	1153
28	1128	1128	1125	1128	1125	1125	1127	1130	1128
29	1100	1100	1095	1100	1095	1095	1099	1099	1098
30	1070	1075	1070	1075	1070	1070	1073	1075	1070
31	1030	1025	1020	1020	1020	1020	1024	1025	1030
32	1002	1002	1000	1005	1000	1000	1002	—	1000
33	982	982	W	—	980	W	980	—	W
34	958	960	W	W	955	955	953	—	W
35	930	930	930	930	935	930	931	930	930
36	918	918	910	915	910	910	917	—	915
37	890	890	885	890	885	885	889	885	890
38	879	879	W	W	W	—	879	—	—
39	840	840	W	W	840	840	840	—	W
40	810	810	807	810	808	805	809	805	810
41	760	760	—	755	760	760	760	—	760
42	750	750	745	750	W	—	750	750	750
43	720	720	723	720	720	720	720	718	720
44	700	700	700	700	695	700	698	695	698
45	665	665	660	665	660	660	663	660	665
46	605	605	—	W	—	605	606	—	—
A <sup>b</sup>	46	41	35	39	40	37	43	26	32
B <sup>b</sup>	46	35	36	38	40	37	43	26	32

<sup>a</sup>Roman numerals designate collaborating laboratories; W = weak (unevaluated) peaks.

<sup>b</sup>A = total number of peaks in International Chemical Reference Substances;

B = total number of peaks in commercial samples.

Table 3. Diazepam

Peaks	Wave numbers in cm <sup>-1</sup>								
	I <sup>a</sup>	II	III	IV	V	VI	VII	VIII	IX
1	—	3440	3420	—	—	3440	3939	—	3440
2	3062	3062	3056	3070	3070	3070	3056	3060	3060
3	3020	3020	W	W	3020	3020	3020	—	3020
4	2978	2978	2970	2970	2970	2970	2970	2970	2978
5	2950	W	W	W	2940	2940	2940	—	W
6	2916	2916	W	2916	2910	2920	2912	2910	2916
7	2840	2840	2830	2835	2835	2835	2837	2840	2840
8	1925	1920	1920	1920	1920	1920	1923	—	—
9	1685	1680	1685	1685	1685	1675	1684	1690	1685
10	1605	1600	1605	1605	1605	1595	1605	1605	1610
11	1575	1570	1570	1565	1572	1565	1573	1750	1575
12	1560	1555	1555	1555	1556	1550	1557	—	1560
13	1485	1482	1480	1485	1480	1475	1482	1480	1485
14	1470	—	W	W	W	W	—	—	—
15	1450	—	—	W	W	W	—	—	1450
16	1440	1440	1440	1440	1440	1440	1442	1440	1442
17	1420	1415	1415	1420	1415	1418	1415	1415	1420
18	1400	1400	1400	1400	1400	1395	1400	1395	1402
19	1340	1340	1340	1340	1340	1335	1339	1340	1342
20	1322	1320	1320	1325	1320	1320	1322	—	1322
21	1315	1312	1310	1312	1312	1310	1314	—	1312
22	1298	1298	1295	1300	1298	1292	1298	W	1298
23	1271	1271	1272	1271	1271	1271	1271	W	1270
24	1261	1255	1252	1255	1255	1250	1255	1255	1255
25	1200	1200	1200	1200	1200	1200	1201	1999	1200
26	1180	1180	1178	1180	1180	1175	1179	1180	1180
27	1167	1160	1165	1165	1165	1162	1167	—	1167
28	1140	1142	—	1140	1140	1140	1140	1140	1140
29	1127	1128	1125	1130	1125	1125	1128	1125	1127
30	1100	1100	1098	1105	1100	1100	1102	1102	1102
31	1075	1075	1070	1075	1070	1070	1074	1070	1073
32	1030	1030	W	1030	1028	1030	1028	1030	1030
33	1020	1020	1020	1020	1020	1020	1020	1020	1020
34	998	998	995	1000	995	995	998	995	998
35	985	985	980	975	980	980	985	980	985
36	950	950	—	950	948	945	950	945	—
37	940	945	940	945	938	938	940	—	940
38	915	915	912	915	915	915	915	912	915
39	890	887	880	890	885	885	887	885	887
40	840	835	840	840	835	840	837	830	840
41	812	812	810	815	812	810	814	810	812
42	790	790	782	789	789	785	787	—	787
43	760	760	760	760	760	760	760	—	760
44	740	740	735	740	740	740	737	737	740
45	705	705	705	705	705	705	706	705	705
46	660	660	660	660	660	660	659	660	659
47	630	630	630	630	630	630	631	625	630
A <sup>b</sup>	46	44	39	42	44	45	45	32	41
B <sup>b</sup>	46	44	39	42	43	44	—	32	41

<sup>a</sup>Roman numerals designate collaborating laboratories; W = weak (unevaluated) peaks.

<sup>b</sup>A = total number of peaks in International Chemical Reference Substances;

B = total number of peaks in commercial samples.

Table 4. Hydrocortisone

Peaks	Wave numbers in cm <sup>-1</sup>								
	I <sup>a</sup>	II	III	IV	V	VI	VII	VIII	IX
1	3430	3430	3420	3430	3430	3410	3429	very wide	3430
2	2970	2970	2958	2970	2970	2955	2970	3000	W
3	2937	2938	2922	2934	2930	2920	2934	2930	2937
4	2915	2910	2902	2914	2910	2900	2912	—	2915
5	1712	1710	1709	1710	1710	1700	1712	1710	1712
6	1645	1642	1640	1645	1642	1642	1642	1645	1650
7	1630	—	W	W	—	W	W	—	W
8	1619	1619	1607	1610	1610	1600	1610	—	W
9	1452	1450	1447	1453	1450	1445	1452	—	1450
10	1432	1430	1430	1433	1430	1425	1431	—	1432
11	1412	1410	W	1410	1410	1405	1410	—	1412
12	1390	1390	1385	1392	1385	1385	1390	—	1390
13	1380	1375	—	W	—	W	1380	—	W
14	1362	1360	W	1360	1360	1360	1361	—	—
15	1349	1347	1347	1348	1345	1340	1347	—	1349
16	1321	1320	1315	1322	1320	1315	1321	—	1321
17	1270	1270	1272	1273	1268	1270	1270	1275	1270
18	1236	1240	1234	1238	1235	1232	1236	1230	1234
19	1225	1225	1220	1225	1220	1220	1222	—	—
20	1203	1203	1200	1202	1198	1198	1201	1185	—
21	1190	W	1195	W	W	1190	W	—	1190
22	1165	1165	1160	1168	1165	1160	1165	1160	1160
23	1132	1132	1130	1125	1130	1128	1132	1130	1132
24	1114	1115	1110	1115	1110	1105	1114	1110	1114
25	1095	1095	W	1098	1092	1092	1096	—	1095
26	1058	1058	1057	1060	1055	W	1058	—	1060
27	1045	1045	1045	1045	1045	1042	1045	1050	W
28	1030	1030	W	1032	1028	1025	1031	1030	1032
29	1005	1005	1007	1005	1005	1005	1005	1000	1005
30	985	985	980	985	985	984	985	985	985
31	965	965	962	968	962	965	965	960	965
32	942	940	947	945	940	942	942	W	942
33	920	915	912	915	915	915	916	W	915
34	900	900	897	902	895	900	899	895	900
35	890	890	887	895	895	890	891	—	890
36	862	862	860	857	860	860	864	860	862
37	830	835	—	W	W	W	830	—	830
38	800	795	W	W	W	W	800	—	798
39	780	780	777	780	780	780	780	780	780
40	745	745	742	745	745	745	745	740	745
41	700	700	W	700	695	700	699	695	695
42	645	645	642	650	645	650	647	—	645
A <sup>b</sup>	42	42	34	38	38	37	41	22	34
B <sup>b</sup>	42	42	—	37	36	37	38	21	34

<sup>a</sup>Roman numerals designate collaborating laboratories; W = weak (unevaluated) peaks.

<sup>b</sup>A = total number of peaks in International Chemical Reference Substances;

B = total number of peaks in commercial samples

## Annex 5

### GUIDANCE FOR THOSE PREPARING OR COMMENTING ON MONOGRAPHS FOR INCLUSION 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:<sup>1</sup>

“(a) to provide specifications on the purity and potency of essential drug substances, widely-used excipient materials, and related 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 on 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 connexion with dosage forms; and

“(e) to present all these elements in such a manner that the *International Pharmacopoeia*, or selective parts of it, can be officially adopted by any Member State [of the World Health Organization].”

To meet some of these aims it is suggested that<sup>2</sup>

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

<sup>1</sup> WHO Technical Report Series, No. 681, 1982 (*WHO Expert Committee on Specifications for Pharmaceutical Preparations*: twenty-eighth report), section 1.2.1.

<sup>2</sup> The present guidelines refer only to drug substances; guidelines referring to specific dosage forms will be issued separately.

2. Where infrared spectrophotometry is regarded as essential for the appropriate identification of a substance an alternative series of tests should always be given. It is recognized that, at the present time, it will be necessary to establish a reference substance whenever infrared spectrophotometry is invoked.

3. In the alternative series of identification tests it is often useful to employ the solvent system of TLC used in the test for related substances for identification purposes as well; 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. Melting point determinations are often useful as identification tests but should not be invoked if the melting temperature is above 200 °C. The combination of tests proposed should provide reasonable assurance that the contents of a container are consistent with the statement on the label.

5. All monographs should preferably contain some chromatographic test to demonstrate freedom from undue quantities of manufacturing or degradation impurities. Wherever possible, this should be effected by thin-layer chromatography using the "high-low system", i.e., by applying the substance being examined at a reasonably high loading and comparing any secondary spots obtained from the material with an appropriately lower loading of the substance being examined. 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 fluorescent plates and examining under an ultraviolet lamp having a maximum output at about 254 nm. In general, it is desirable to choose a system such that the principal spot shows an  $R_f$  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.

6. Gas-liquid chromatography or high-pressure 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.

7. 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.

8. Chloride and sulfate limit tests should be invoked only when (a) it is impossible to control more relevant impurities in a direct fashion;

(b) it is necessary to guard against confusion between chloride and sulfate salts of a particular base; or

(c) some special justification for the inclusion of such tests can be made.

9. Where it is necessary to control the acidity or alkalinity of a material, 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 substance being tested does not show a marked buffering effect.

10. Requirements for clarity of solution should, in general, be invoked whenever the product being examined is intended for potential injectable use. 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 should preferably be titrimetric or spectrophotometric. Emphasis should, wherever possible, be placed on precise assays, even though they may not be very specific. Specificity is conferred by the combination of other tests in the monograph.

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 usage 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 thin-layer chromatography, since the composition of such phases is liable to change if volatile solvents are included.

14. Existing pharmacopoeial methods should be invoked wherever 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.

## COLLABORATION WITHIN THE BASIC TEST PROGRAMME

### Introduction

In its twenty-eighth report, the WHO Expert Committee on Specifications for Pharmaceutical Preparations agreed that the prime objectives of basic (or simplified) tests for pharmaceutical products, which was the subject of preliminary discussions in the Committee's twenty-sixth and twenty-seventh reports, should be as follows:

“(a) to provide simple and readily applicable methods for verifying the identity of active ingredients using a limited range of readily available reagents;

(b) to provide a practicable means for confirming the identity of a drug, where fully equipped laboratories are not available;

(c) to provide a means for rapid verification of the identity in cases where each container of a large consignment has to be identified (full quality assessment of such a consignment is usually carried out only on a mixed sample from various containers); and

(d) to indicate if gross degradation has occurred in certain substances that are known to decompose readily under adverse conditions.”

It was noted that basic tests are not, in any circumstances, intended to replace the requirements of pharmacopoeial monographs. The latter give an assurance of quality whereas basic tests *merely confirm* the identity.

The test procedures for pharmaceutical substances elaborated so far are contained in the unpublished document WHO/PHARM/81.506/Rev. 1. The procedures for the *confirmation of the identity* consist of one or more test-tube identification reactions based upon colour, precipitate, or fluorescence, and on data regarding the physical aspects of the substance, its melting characteristics, and frequently the melting point of eutectic mixtures.

The test procedures for the *indication of gross degradation* consist of one or more simple tests based on the description of physical aspects, solubility, or test-tube reactions. These tests have been developed during the course of stability testing carried out under

standardized conditions in air at temperatures of 50 °C and 70 °C and 100% humidity, with light excluded. The tests are intended to provide evidence of degradation of 10% or more.

In addition to the test-tube reactions and melting point determinations, procedures based on thin-layer chromatography have been developed and are contained in the unpublished WHO document Pharm. S. 636.

Attached is a protocol for guidance in the development and the verification of basic tests.

## **Protocol for the Development and Verification of Basic Tests**

### **1. Development of tests**

(a) Tests for each drug substance and the corresponding dosage forms should, whenever possible, be developed together by the same person. Only *one* person should be asked to develop tests for a specific drug substance and/or dosage form.

Where suitable tests are contained in *The international pharmacopoeia* these should be given priority, and the description should not be unnecessarily modified.

(b) In order to secure appropriate distribution of work, each investigator should compile a list of locally available drug substances.

(c) When a proposed test proves to be inadequate in the course of validation in other laboratories, the information will be referred back to the prime investigator who will have the responsibility of devising an alternative test. To this end, all samples used in the course of validation of the tests should be supplied to the prime investigator, where appropriate through WHO.

Priority should in each case be given to tests based on test-tube reactions and melting characteristics.

The test-tube reactions can involve colour reactions, fluorescence, or precipitations.

The following methods are recommended in order to introduce some homogeneity among the reactions used in basic tests:

Element or active functional group	Principle of the reaction
chloride or hydrochloride	<ul style="list-style-type: none"> <li>- precipitation with <math>\text{AgNO}_3</math></li> <li>- in order to complete the characterization of the formed silver chloride it is always preferable to separate the <math>\text{AgCl}</math> before verifying its dissolution in ammonia (otherwise precipitation of other bases may occur in alkaline medium)</li> </ul>
bound chlorine	<ul style="list-style-type: none"> <li>- ignition with <math>\text{Na}_2\text{CO}_3</math> then reaction with <math>\text{AgNO}_3</math> after acidification</li> </ul>
fluoride and bound fluorine	<ul style="list-style-type: none"> <li>- inhibition of wetting the inner wall of a tube containing a chromic acid/sulfuric acid mixture</li> </ul>
sulfate	<ul style="list-style-type: none"> <li>- precipitation with <math>\text{BaCl}_2</math></li> </ul>
bound sulfur	<ul style="list-style-type: none"> <li>- fusion with <math>\text{NaOH}</math> or <math>\text{Na}_2\text{CO}_3</math>, then reaction with <math>\text{BaCl}_2</math> after acidification with <math>\text{HCl}</math></li> </ul>
heterocyclic sulfur	<ul style="list-style-type: none"> <li>- heating with <math>\text{Zn}</math> and <math>\text{HCl}</math> : formation of dihydrogen sulfide detected with lead acetate paper</li> </ul>
sodium ion	<ul style="list-style-type: none"> <li>- precipitation with magnesium uranyl acetate</li> </ul>
potassium ion	<ul style="list-style-type: none"> <li>- precipitation with sodium cobaltinitrite</li> </ul>
saturated compounds	<ul style="list-style-type: none"> <li>- absence of decolorization of bromine (obtained from <math>\text{KBr} + \text{KBrO}_3 + \text{HCl}</math>)</li> </ul>
reducing compounds	<ul style="list-style-type: none"> <li>- formation of a red precipitate in a warm solution with potassio-cupric tartrate</li> <li>- formation of a silver mirror in ammoniacal solution with silver nitrate</li> </ul>
multiple bonds (double or triple)	<ul style="list-style-type: none"> <li>- in alkaline medium permanganate changes to brown</li> </ul>
glycol	<ul style="list-style-type: none"> <li>- precipitation of silver iodate produced by the reaction of silver periodate</li> </ul>
enolizable ketone	<ul style="list-style-type: none"> <li>- coloration produced with nitroprusside and <math>\text{NaOH}</math></li> </ul>
phenol	<ul style="list-style-type: none"> <li>- coloration produced with the diazonium salt of the sulfanilic acid in alkaline medium</li> <li>- coloration with a ferric salt (various colorations) are also obtained with the same reagent, such as for: formate and acetate ions, benzoate ion, acetylacetone and enolizable ketones, phenazone, camphocarbonylic acid, colchicine, phenylpyruvic acid, hydroxyacids, amino acids</li> <li>- coloration produced by the reaction of a primary aromatic amine and hypochlorite</li> </ul>

Element or active functional group	Principle of the reaction
ortho diphenol	– coloration of the molybdate ion in acidic medium
aliphatic amine and amino acid	– coloration with triketohydrindene hydrate (ninhydrin) and pyridine
amino acid	– colored precipitate with cupric ion and NaOH
primary aromatic amine	– coloration with dimethylaminobenzaldehyde in acidic medium – diazocoupling by action of nitrite ion in acidic medium followed by 2-naphthol in alkaline medium – coloration produced with phenol and hypochlorite
aromatic nitro compounds	– reaction with zinc in acidic medium and identification of the amine using one of the reactions described above
ammonium salts or aliphatic amine	– reaction with NaOH, the vapours of the liberated base being detected with pH-indicator paper
alkaloid or nitrogenous bases with high molecular weights	– precipitate with potassio-mercuric acetate
ester	– reaction with hydroxylamine, then detection of the formed hydroxamic acid by coloration obtained by adding a ferric salt – odour of ethyl acetate on heating with sulfuric acid and ethanol
complex polyhydroxylated or polyunsaturated structures	– coloration formed with phosphoric acid – coloration formed with sulfuric acid alone, or with the addition of nitrous/nitric acid mixture, molybdate, dichromate, or formaldehyde
xanthine	– heating to dryness of the substance with HCl and hydrogen peroxide, then coloration produced with the reaction of ammonia on the residue
barbiturate	– coloration produced with a cobalt salt in ammoniacal solution

## 2. Verification of tests

(a) Drug substances: If a pharmacopoeial test is selected no verification is required. In other circumstances verification in one laboratory will suffice.

(b) Dosage forms: Verification must be undertaken, in each instance, in at least four different laboratories selected on a representative regional basis. Tests should be undertaken on locally available solid oral dosage forms, branded or generic, containing the substance in question.

### **3. Coordination**

Responsibility for coordination and monitoring of the programme will reside with WHO, which will pay particular regard to reasonable distribution of work among the various collaborators.