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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Twenty-eighth Report

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

Geneva, 14–19 December 1981

Members

- Professor E. A. Babayan, Head of the Department of New Drug Evaluation, Ministry of Health, Moscow, USSR
Dr D. Cook, Acting Director-General, Drugs Directorate, Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada
Dr P. O. Emafo, Director (Pharmaceutical Services), Federal Ministry of Health, Lagos, Nigeria
Dr S. S. Gothoskar, Drugs Controller (India), Directorate General of Health Services, New Delhi, India
Dr L. T. Grady, Director, Drugs Standards Division, The United States Pharmacopeia, Rockville, MD, USA
Mr C. A. Johnson, Secretary and Scientific Director, British Pharmacopoeia Commission, London, England
Professor J. Laszlovszky, Scientific Adviser, National Institute of Pharmacy, Budapest, Hungary
Dr M. Pesez, Scientific Adviser, Roussel-Uclaf SA, Romainville, France (*Chairman*)
Dr N. Rofael, Director, Pharmaceutical Control and Research Laboratories, National Organization for Drug Control and Research, Cairo, Egypt (*Rapporteur*)
Mr Tu Guoshi, Chief, Division of Pharmaceutical Chemistry, National Institution for the Control of Pharmaceutical and Biological Products, Ministry of Health, Beijing, China (*Vice-Chairman*)

Secretariat

- Dr J. F. Dunne, Acting Chief Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland
Professor K. Hartke, Director, Institute for Pharmaceutical Chemistry, Marburg University, Marburg/Lahn, Federal Republic of Germany (*Temporary Adviser*)
Dr S. Kliouev, Senior Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland
Mr B. Öhrner, Deputy Director, WHO Collaborating Centre for Chemical Reference Substances, Solna, Sweden (*Temporary Adviser*)
Dr P. R. Pabrai, Director, Central Indian Pharmacopoeia Laboratory, Ghaziabad, India (*Temporary Adviser*)
Miss M. Schmid, Technical Assistant, Pharmaceuticals, WHO, Geneva, Switzerland
Professor O. Sylla, Technical Adviser to the Ministry of Health, Faculty of Medicine and Pharmacy, Dakar, Senegal (*Temporary Adviser*)
Miss A. Wehrli, Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland (*Secretary*)

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-eighth Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 14 to 19 December 1981. The meeting was opened on behalf of the Director-General by Dr Ch'en Wen-chieh, Assistant Director-General, who stressed that a considerable increase in the provision of essential drugs was crucial to the effective application and extension of primary health care. Essential drugs have not only to be available, but should also be safe and effective. To this end their quality must be assured. Indeed, the provision of adequate quality control must be regarded as a critical element in the broader objective of providing effective health care delivery by the year 2000. While the "Certification scheme on the quality of pharmaceutical products moving in international commerce", adopted by the Twenty-eighth World Health Assembly in resolution WHA28.65 (I), provides valuable safeguards in relation to imported products, it is also important to offer countries some guidelines on how to develop their own quality control facilities as effectively as possible, having regard both to the resources available to them and to their specific needs.

1. THE FUTURE OF THE *INTERNATIONAL PHARMACOPOEIA*

1.1 National and regional pharmacopoeias

Most national and regional pharmacopoeias provide specifications on purity and potency which form the legal basis for the control of pharmaceutical products. With the introduction of new therapeutic substances and the growth of national registration and inspection systems, the role of pharmacopoeias has evolved so that they are now of greater importance than formerly. They provide standards that are publicly available and that allow independent evaluations of drug quality to be made at any stage after the drugs have left the manufacturer's care and prior to their utilization.

1.2 The *International Pharmacopoeia*

The *International Pharmacopoeia* provides internationally acceptable standards for the purity and potency of pharmaceutical products moving in international commerce that are available for adoption by Member States in accordance with Articles 21 (d) and 23 of the Constitution of the World Health Organization (2) and resolution WHA3.10 of the Third World Health Assembly (3).

Many national or regional pharmacopoeias rely increasingly on complex techniques of analysis that require expensive equipment and highly specialized personnel, but these methods are inapplicable in countries lacking these resources; and for the most part, they merely permit analyses to be carried out more rapidly than by the classical chemical methods.

Whereas earlier editions of the *International Pharmacopoeia* had relied heavily on material taken from certain national pharmacopoeias, the third edition (4), now in the course of publication in several volumes, aims to accommodate the needs of developing countries by offering sound standards for the essential drugs (5), which rely (wherever possible) on classical procedures. Volume 1, which became available in 1979, describes the general methods of analysis, while volume 2, published in 1981, contains quality specifications for 126 essential drug substances. Monographs on the remaining substances in the WHO model list of essential drugs (5) will be included in volume 3; several of these have not, as yet, been published in a national pharmacopoeia.

It is envisaged that volume 4 will include monographs on widely used excipients and dosage forms for essential drugs. The latter is a demanding objective. The use of a wide range of interchangeable excipients in finished products, and particularly in solid unit-dosage forms, creates difficulties because some of these substances are liable to interfere with the results of established and published pharmacopoeial methods. These difficulties are evident at national level; on a worldwide basis, they are compounded because of the greater number of excipients to be accommodated. None the less, the need to provide quality control laboratories in developing countries with guidance on the testing of final dosage forms is evident.

Accordingly, methods and proposed standards for identity, assay and impurity patterns of individual dosage forms of essential drugs will be developed wherever feasible. The proposed standards will first be tested on finished products of local manufacture in collabora-

ting laboratories in various parts of the world. On the basis of a survey of the results obtained, necessary adjustments will then be made to the original proposals to broaden their applicability.

To the same end, additional general advice on extraction and separation procedures will be included in the existing general monograph on solid oral dosage forms (6). This will permit a greater variety of dosage forms to be tested than is currently possible by application of national pharmacopoeial monographs.

1.2.1 Summary

Believing that the role and objectives of the *International Pharmacopoeia* are still not widely appreciated, the Committee urged that all possible means should be adopted to correct the position.

In summary, the functions and characteristics of the *International Pharmacopoeia* are:

(a) to provide specifications on the purity and potency of essential drug substances, widely-used excipient materials, and related dosage forms (5). 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 selected parts of it, can be officially adopted by any Member State.

Inter alia, the production of the *International Pharmacopoeia* helps to advance the setting of pharmacopoeial standards at national level,

in that it fosters a valuable exchange of experiences gained in a wide variety of countries.

2. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

2.1 Reports from the WHO Collaborating Centre

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

2.1.1 *Establishment of new reference substances*

The following new International Chemical Reference Substances have been established:

anhydrotetracycline hydrochloride	nicotinamide
benzylpenicillin potassium	nicotinic acid
4-epianhydrotetracycline hydrochloride	sulfamethoxazole
4-epitetracycline ammonium salt	sulfanilamide
ethosuximide	tetracycline hydrochloride
(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine	trimethoprim
methyl dopa	

2.1.2 *Replacement of current reference substances*

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

benzylpenicillin sodium	hydrocortisone acetate
dexamethasone	vitamin A acetate
griseofulvin	

The Committee noted with satisfaction that the analytical reports of the Centre had now been expanded to include more of the results obtained in the course of examination of the substances, as well as data submitted by the manufacturers. Information provided in confidence to the Centre by manufacturers cannot be revealed but all available information is taken into account in the assessment of the suitability of the proposed International Chemical Reference Substances.

¹ WHO Collaborating Centre for Chemical Reference Substances. *Report on the work in 1979* (unpublished document WHO/PHARM/80.504); *Report on the work in 1980* (unpublished document WHO/PHARM/81.508).

2.1.3 *Distribution of reference substances*

Following a reduction in the number of requests for International Chemical Reference Substances during 1979, demand has again risen. In particular, a higher proportion of requests for reference substances was now being received from developing countries, which indicates progress in drug quality control programmes in these countries.

The Centre still encounters difficulties in sending reference substances to certain countries. For example, a number of consignments of reference materials have been seriously delayed or lost in transit, whereas others have been held up unduly (while awaiting customs clearance) and have probably been stored in conditions that could adversely affect the quality of the reference substances. It is expected that the frequency of customs delays will increase further. As more substances become scheduled under the Convention on Psychotropic Substances 1971 (7), many countries will impose more stringent controls on their shipment. The Committee recommended that the Centre be assisted in finding a solution to these problems and that the possibility be explored of obtaining international agreement that would relieve the International Chemical Reference Substances from all import taxes and customs restrictions. Although such arrangements already exist on a regional basis, the difficulties of achieving a satisfactory global agreement were acknowledged. To provide an interim solution, it was suggested that laboratories—now having to contend with these difficulties—should request the responsible national authority to minimize the obstacles. WHO might, in some instances, alleviate the position by arranging the shipment of International Chemical Reference Substances through its network of regional offices and national programme coordinators.

2.1.4 *International cooperation*

Collaboration had been further developed between the Centre and the various responsible organizations that establish national and regional pharmaceutical reference materials. The valuable contribution that these organizations and various pharmaceutical manufacturers offer to the WHO programme on International Chemical Reference Substances was gratefully acknowledged and the Committee recommended that, where possible, international cooperation should be further extended.

The advice and training that the Centre had provided, despite limited resources, to a number of countries that were about to establish their own national or regional reference materials was noted with appreciation. The Committee considered this aspect of the Centre's work to be highly important and emphasized the need to obtain further support for the Centre so that it could continue these activities.

2.1.5 *Future work*

The Committee endorsed the International Chemical Reference Substances established to date and the proposed programme of work for providing further reference substances as required. The Centre had also received a number of requests for reference substances of various impurities liable to occur in medicinal substances. Such materials should not commonly be required, but in a few instances they are necessary to control particularly important impurities. These are of two different types: starting materials and intermediates generated during synthesis on the one hand, and degradation products formed during improper storage on the other. The provision of reference substances for the first class of compounds would not present any particular problem since they are usually commercially available. However, synthesis of degradation products, when undertaken at all by the manufacturers, is usually performed on a very small scale and the methods are rarely published. When such substances are not obtainable in the quantities required for their establishment as International Chemical Reference Substances, it would be of value if the methods of synthesis of these compounds could be obtained from the manufacturers for transmittal through the Centre to any interested control laboratories.

A study will be undertaken by the Centre to investigate whether the present reference preparation of vitamin A, which is a solution of vitamin A acetate in vegetable oil dispensed in gelatine capsules, can be replaced by pure vitamin A acetate in crystalline form, which would have a better storage stability.

The Committee was unanimous in its expression of thanks to the Centre and to the National Corporation of Swedish Pharmacies, which sponsors the Centre's activities; in particular, appreciation was expressed for the individual attention that had been offered to correspondents and visitors.

2.2 General guidelines for the establishment, maintenance and distribution of chemical reference substances

2.2.1 Revision of guidelines

A revised version of the guidelines, originally published in the twenty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (8), was endorsed by the Committee and is attached to this report (Annex 1). These guidelines now include an additional section on the need for national and/or regional collections because of the situation described in the next section.

2.2.2 National or regional reference substances

Because the WHO Collaborating Centre at Solna, Sweden, may not be in a position to meet all future demands, and because customs difficulties can delay the shipment of materials, it might be desirable to establish reference materials that have been calibrated against the International Chemical Reference Substances to meet national or regional requirements.

The establishment of local collections of reference materials would, however, pose problems. The meticulous work carried out at the WHO Collaborating Centre to establish the international collection would have to be matched in local or regional laboratories, and for this an adequate training programme would be required. Both the Collaborating Centre and other laboratories concerned with the evaluation and establishment of reference materials could provide this training—subject, however, to the availability of necessary resources. In some measure, the training requirements could be met by the preparation of teaching aids (see section 6).

Distinct advantages would accrue if the requests from national or regional authorities for given reference materials were coordinated through the World Health Organization. This would make it simpler for the manufacturers to respond to these requests and to reduce the number of batches from which these materials derive.

2.2.3 Reference substances required in connexion with the registration of new drugs

Reference substances are sometimes required when a drug is considered for initial registration. In these situations, the manufacturer should be prepared to furnish to the national drug registration au-

thorities both a sample of the reference material and a protocol setting out (in the kind of detail now provided within the annual reports of the WHO Collaborating Centre) the justification for regarding the material as being of the requisite standard.

2.2.4 Alternatives to the use of reference substances

Considering the economic factors, alternative procedures for establishing specifications that do not require the use of reference materials should be explored whenever possible. For example, the adequacy of infrared reference spectra, as substitutes for reference substances, should be evaluated in an international context, as advocated in the Committee's twenty-seventh report (6).

3. BASIC TESTS FOR PHARMACEUTICAL SUBSTANCES AND DOSAGE FORMS

3.1 The role of basic tests¹

The Expert Committee agreed that the prime objectives of basic tests for pharmaceutical products, which was the subject of preliminary discussions in the Committee's twenty-sixth (9) and twenty-seventh reports (6), 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 the various containers); and

(d) to indicate if gross degradation has occurred in certain substances that are known to decompose readily under adverse conditions (see section 3.3).

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.

¹The term "basic tests", although not entirely satisfactory, has been retained in this report in English because it has gained wide currency; there are also problems in translating it into other languages. In some languages an equivalent term has been established by WHO.

3.2 Progress in developing basic tests

3.2.1 *Test-tube and melting-point techniques*

3.2.1.1 *Pharmaceutical substances.* Protocols setting out suggested procedures have been produced by collaborating scientists for 253 substances. In each case, these protocols provide data on the physical aspects of the substance, its melting-point—and frequently the melting-point of eutectic mixtures—and one or more test-tube identification reactions based upon colour, precipitate or fluorescence.

The suggested procedures¹ have been established and verified by specialists from several collaborating laboratories in drug control institutions and colleges of pharmacies under widely diverse climatic conditions. Tests for 198 substances were verified in one or more laboratories, and the 55 remaining substances will be subjected to examination during the next year.

It was recommended that the tests already accepted should be published as soon as possible, and that test procedures for other substances should now be devised.

3.2.1.2 *Dosage forms.* Verification of the identity of active substances in dosage forms by test-tube reactions or melting characteristics is more problematic than the testing of the identity of individual raw materials. Excipients are liable to interfere, and their identity may be unknown to the analyst. Ingenuity is therefore needed in devising simple and reliable tests for dosage forms. Basic tests will initially be established only for simple dosage forms containing one active ingredient. In each case, the applicability of the proposed procedures will need to be confirmed in many countries before they can be published as firm international recommendations.

In accord with the objective of simplicity, the tests for dosage forms should be devised so that they may be carried out directly on the ground material (in the case of solid dosage forms), or by the direct action of reagents in solution.

A highly promising technical approach is a simple isolation procedure known as the “strip-test”. A strip of filter-paper is inserted for a few minutes into a suspension of the powdered test material in

¹ *Basic tests for pharmaceutical substances* (unpublished document WHO/PHARM/81.506).

a selective solvent. The section of the strip which was in contact with the suspension is then cut off and the required reaction is carried out on the remaining part that had been wetted by capillary action. All insoluble excipients are thus eliminated from the reaction.

The test sheets describe how the sample should be prepared, as either a solution, or a powder, or both. A variety of independent identity tests are provided, which are (if possible) drawn from the tests for the active substance.

The test sheet indicates the amount of active substance required for reliable performance of the test, which is particularly important when the test preparation is available in a wide variety of strengths.

An initial compilation of test sheets for dosage forms, prepared by several specialists, was produced early in 1981.¹ It contains 112 test sheets for individual dosage forms of 106 pharmaceutical substances.

New test sheets will be prepared as soon as possible. The verification of these proposed procedures will be carried out by at least four laboratories located in developing countries.

3.2.2 *Thin-layer chromatographic techniques*

The use of thin-layer chromatography (TLC) as a simplified procedure for the verification of the identity of active ingredients was considered separately from other techniques. In principle, this technique could completely or partially replace other methods, but certain difficulties will need to be resolved before it can be incorporated in the basic test programme.

Firstly, the technique has the inherent disadvantage that it is dependent upon the availability of authenticated reference specimens. Secondly, some of the existing widely used solvent systems may be too volatile for use in laboratories in tropical countries.

3.2.2.1 *Pharmaceutical substances.* TLC procedures for 103 substances² were produced in 1981. These involved the use of 6 different adsorbents (6 types of plates coated with either silica gel or cellulose), 34 solvent systems (composed of 26 different solvents), and 5 methods of detection (iodine vapours, ultraviolet light, and 3 spray reagents).

¹ *Basic tests for pharmaceutical dosage forms* (unpublished document PHA/EC/81.10).

² *Basic test procedures involving the use of thin-layer chromatography for pharmaceutical substances* (unpublished document PHA/EC/81.9).

Although the number of substances considered in these studies is only one-third of the total in the programme, these results indicate that the number of adsorbents and established detection methods are adequate to sustain a simplified system. But further work is now required to rationalize the procedures so that the number of individual solvents is reduced to about 15.

3.2.2.2 *Dosage forms.* It is probable that the tests developed for the active substances may be readily adapted for the verification of the identity of dosage forms. Success will depend upon the exclusion of interfering excipients by adequate extraction procedures.

3.3 Stability study on pharmaceutical substances

Little information has been published on the degradation of long-established pharmaceutical substances (except for obviously unstable products) and, in many instances, their behaviour, when exposed to extreme climatic conditions, is uncertain. By contrast, much information on the stability of newly introduced substances is available, since this information is a mandatory requirement in many countries for registration of a new product and for determining expiry dates.

The work done so far was carried out under the following standardized conditions: 30 days' exposure to air at a temperature of 50 °C and a relative humidity of 100%. The appearance of degradation products was detected by thin-layer chromatography, supplemented (as necessary) by spectrophotometry, fluorescence reactions, high-pressure liquid chromatography, and chemical determinations. The substance was additionally exposed to a temperature of 70 °C under the same humidity conditions for a further period of 3–5 days. When negative, these results provided conclusive proof of the stability of the substance even under highly adverse conditions. All tests were carried out with light excluded, because it is easy to protect the substances from light during storage.

The results of the study were collected in two unpublished documents;¹ 256 substances were tested, of which 96 were degradable

¹ 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). Details of the procedures used in these stability studies can be obtained from Pharmaceuticals, Division of Diagnostic, Therapeutic and Rehabilitative Technology, World Health Organization, 1211 Geneva 27, Switzerland.

under the conditions employed. Simple tests for each of these 96 substances were developed which reliably demonstrated 10% of degradation, and these have been incorporated into the basic test sheets and will be considered when specifications are prepared for the *International Pharmacopoeia* (4).

4. STRUCTURE AND MANAGEMENT OF A NATIONAL DRUG CONTROL LABORATORY

Drug quality control laboratories are an important element for quality assurance in pharmaceutical supply systems (6). Such laboratories can be simple, yet effective. None the less, provision should be made for their enlargement and for increasing complexity as experience is gained and as circumstances demand. When the resources are inadequate to provide for comprehensive control, attention should be concentrated on the most widely used products and on those presenting a potential problem.

The Committee recommended that a detailed review of the principles that should determine the structure and management of a national drug control laboratory should be undertaken. The principal aspects requiring study are:

- (a) the size and structure of the laboratory, considering the available resources and extent and pattern of drug consumption;
- (b) personnel requirements, in terms of both trained and supporting staff;
- (c) the equipment necessary for the required scope of activities, and the need to ensure, before ordering expensive equipment, that facilities for its maintenance are available;
- (d) the reagents, calibration and maintenance of instruments, and general stock-keeping;
- (e) the types of material to be sampled (concentrating on drugs of high risk), the methods for obtaining representative samples, and the standard operational procedures to be followed for testing, record-keeping and sample retention;
- (f) the validation of analytical procedures and the definition of responsibilities for initiating action based on the results obtained; and
- (g) management responsibilities for the laboratory, including guidelines on the safety aspects.

5. PRECAUTIONS DURING STORAGE AND TRANSPORT OF PHARMACEUTICAL PREPARATIONS

Because improper storage, packaging and handling of pharmaceutical substances and dosage forms can present hazards, relevant guidelines have to be prepared. These should be complemented by a list of pharmaceutical substances that are most susceptible to deterioration in extreme climatic conditions.

6. TRAINING ACTIVITIES

The Committee strongly recommended the training of personnel for quality control activities through (a) group training courses and (b) individual training.

Group training courses should continue to have high priority, and pharmaceutical companies and funding agencies should be encouraged to provide funds for this purpose. In addition, suitable teaching material (cassettes, audiovisual aids, etc.) should be developed with WHO's assistance. The training offered in these courses should result in immediate application by the trainees on return to their posts. It should thus have relevance to their main duties and take into account the laboratory facilities available to them, and should be consonant with the objectives of the WHO programme on essential drugs (5).

The Committee noted with satisfaction the offer, to personnel in developing countries working in national control laboratories, by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), of individual training of 3–6-month periods in the quality control laboratories of pharmaceutical companies (10).

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Annex 1

GENERAL GUIDELINES FOR THE ESTABLISHMENT, MAINTENANCE, AND DISTRIBUTION OF CHEMICAL REFERENCE SUBSTANCES

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1. CRITERIA FOR DETERMINING THE NEED FOR THE ESTABLISHMENT OF CHEMICAL REFERENCE SUBSTANCES

The production, validation, maintenance, and distribution of chemical reference substances¹ is a costly and time-consuming undertaking. It is therefore of great importance to limit the work involved by determining in a critical way whether a need for a given substance exists. Requests for new reference substances usually arise because a certain approach to the development of a specification for a new substance or product has been adopted. Methods may have been proposed in a specification that require the establishment of a reference substance for use as a comparative standard and the first matter that should be assessed, therefore, is whether some alternative procedure could be adopted that does not require a comparative standard and that might still be equally satisfactory. For example, an analytical procedure based on a stoichiometric relationship might be as valid, in a given context, as one based on ultraviolet absorption spectrophotometry and would obviate a possible need for a reference substance.

The types of analytical procedure at present used in specifications for pharmaceutical substances and products that may require a chemical reference substance are:

- (a) infrared spectrophotometry, whether for identification or quantitative purposes;
- (b) quantitative methods based on ultraviolet absorption spectrophotometry;
- (c) quantitative methods based on the development of a colour and the measurement of its intensity, whether by instrumental or visual comparison;
- (d) methods based on chromatographic separation for identification or quantitative purposes;
- (e) quantitative methods (including automated methods) based on other separative techniques that depend upon partition of the material to be determined between solvent phases, where the precise efficiency of the extraction procedure might depend upon ambient

¹The term *chemical reference substance*, as used here, refers to an authenticated uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with the properties of a product under examination, and that possesses a degree of purity adequate for its intended use.

conditions that vary from time to time and from laboratory to laboratory;

(f) quantitative methods, often titrimetric but sometimes gravimetric, that are based on non-stoichiometric relationships;

(g) assay methods based on measurement of optical rotation; and

(h) methods that might require a reference material consisting of a fixed ratio of known components (for example cis/trans isomers).

There is a consensus among experts that for certain of the above categories a reference substance is essential. For example, the use of thin-layer chromatography as a means of identification dictates the need for a reference material, because the migration of a substance relative to the solvent front is dependent on the operating conditions: certain of the conditions, such as temperature and composition of the mobile phase, are readily controllable; others, such as the precise thickness and the water content of the layer used and the degree of saturation of the tank, cannot be exactly reproduced. Other examples are non-stoichiometric procedures, such as the iodimetric titration of penicillins and the determination of ascorbic acid by titration with an indophenol.

In other cases, however, differences of opinion exist as to whether a reference substance is essential. It has been proposed, for example, that a reference sample might not be essential for infrared spectrophotometry; instead it might be possible to define certain characteristics of a spectrum or to provide a copy of an "authentic spectrum" that could be used for purposes of comparison. Differences in the mode of presentation of spectra by diverse instruments, differences in resolution between instruments, and problems associated with polymorphism and solvation make such an approach difficult in some instances at the present time. Nevertheless, this approach, implemented where feasible, would significantly reduce the number of reference substances needed and also reduce the extent of use of those substances required for other purposes.

The need for reference substances in ultraviolet absorption spectrophotometry has probably given rise to the greatest controversy. Certain compendia (for example, the *United States Pharmacopeia*) require comparison of observed spectral characteristics of the substance under examination with those of a reference substance similarly treated, while others (for example, the *European Pharmacopoeia*, the *British Pharmacopoeia*, and the third edition of the *International Pharmacopoeia*) rely on comparison with quoted extinction values. Both of these methods have advantages, but neither is above criticism.

A mere comparison of spectra obtained by an operator using poor technique and inadequately maintained equipment might lead to acceptance of a sample but might not constitute a valid assay. Conversely, the use of inadequate controlled conditions and a quoted extinction value might lead to rejection of a satisfactory sample. It must also be accepted that, despite considerable improvements in the stability, accuracy and precision of ultraviolet spectrophotometers during the past decade, variations between instruments still occur and may undermine the validity of using quoted extinction values.

These considerations, which also apply in some measure to other instrumental techniques such as infrared spectrophotometry, make it essential that adequate criteria for instrumental performance should be defined. This, in turn, suggests that a further class of reference materials, designed to assist in the calibration of instruments and the standardization of procedures, is also necessary. For example, the *International Pharmacopoeia* (third edition, vol. 1, p. 35) prescribes the use of standardized didymium or holmium oxide filters for wavelength calibration and standardized potassium dichromate or potassium nitrate for absorbance calibration of ultraviolet spectrophotometers. In the field of standardization of procedures it is recognized that reference materials may be required to calibrate, for example, apparatus for dissolution testing. Such reference materials as these are, however, outside the scope of this present discussion of chemical reference substances.

2. EVALUATION OF REFERENCE SUBSTANCES

Evaluation of the suitability of a material proposed for use as a reference substance requires careful testing. It is necessary to consider all data obtained by examining the material, employing a wide variety of analytical methods. When taken as a whole they give confidence that the material is suitable for the intended use. Depending on the intended use of the substance, testing can be more or less searching and involve a number of independent laboratories.

In the case of reference substances that are intended for use in the identification tests or in the determination of purity, the examination may be carried out without a unified programme, all analytical data obtained in different laboratories being then considered. If compatible results are obtained in all the collaborating laboratories, a positive decision concerning the suitability of the material can be arrived at.

The procedure may be simplified in the case of the evaluation of replacement batches of an existing reference substance.

When it is necessary to assign quantitative values to a reference substance, a collaborative study, following a carefully designed protocol and employing at least three cooperating laboratories, should be undertaken.

3. CHEMICAL AND PHYSICAL METHODS USED IN EVALUATING REFERENCE SUBSTANCES

The methods used to establish a proposed material fall into two broad groups: those intended primarily to identify the material and those to establish the purity. With most methods, the percentage purity of a reference substance cannot be expressed as an absolute value if the impurities have not been identified. In such instances, the quoted purity is an estimate based upon the data obtained by use of the various analytical methods employed to establish the purity of the reference substance.

3.1 Methods useful for verifying the identity of reference substances

The identity of a material that is intended to replace an established reference substance of the same molecular constitution may be verified by means of tests that are capable of demonstrating that the characteristic properties of the two specimens are identical. For this purpose, a comparison of their infrared absorption spectra often suffices. Similarly, where a newly proposed reference substance consists of a compound whose structure has been satisfactorily elucidated, its identity may be confirmed by matching the infrared spectra of the material and of an authentic compound. Other highly specific techniques, such as nuclear magnetic resonance spectroscopy, mass spectrometry, or X-ray diffraction crystallography, may also be used for such comparisons.

However, where no authentic specimen of the proposed reference substance is available for comparison and definitive data about its properties are lacking, it may be necessary to verify the identity of the material by applying several analytical techniques currently used to characterize new compounds. Such analytical methods may include elemental analyses, crystallographic studies, mass spectrometry, nuclear magnetic resonance spectroscopy, functional group analyses,

infrared spectrophotometry, and ultraviolet spectrophotometry, as well as such other supplementary tests as are necessary and sufficient to establish that the proposed reference material is the required substance.

3.2 Purity requirements for reference substances

The purity requirements for a reference substance depend upon its intended use. A reference substance proposed for an identification test by infrared spectrophotometry does not require meticulous purification, because the presence of a small percentage of impurities in the substance often has no noticeable influence on its infrared spectrum. Similarly, reference substances that are applied in low loadings in thin-layer chromatographic tests need not be highly purified.

On the other hand, reference substances that are to be used in assays should preferably possess a high degree of purity. As a guiding principle, a purity of 99.5% or better is desirable for such reference substances, although in cases where the precision of the analytical procedure for which the reference substance is required is low, such a degree of purity may not be necessary. In making a decision about the suitability of a reference substance, the most important consideration is the influence of the impurity on the attribute measured in the assay. Impurities with physicochemical characteristics similar to those of the main component will not impair the usefulness of a reference substance, whereas even traces of impurities with significantly different properties may render a substance unsuitable as a reference substance.

3.3 Methods used in determining the purity of reference substances

A consideration of the methods to be employed in examining a chemical reference substance should take account of its method of preparation and its intended use. Such analytical methods may be divided into two broad categories—those that depend solely upon an intrinsic thermodynamic property of the system (e.g., phase solubility analysis and differential scanning calorimetry), and those that require comparison with an external standard (e.g., chromatographic or spectrophotometric methods). Methods in the former group allow the measurement of total impurity levels in absolute terms but provide little information regarding the molecular structure of the contaminants.

3.3.1 *Methods based on intrinsic thermodynamic properties*

3.3.1.1 *Phase solubility analysis.* Phase solubility analysis may be employed to detect contaminating substances, including isomeric species, and to estimate their concentration. The coefficient of variation that can be achieved using this method is about 0.2%. It is applicable to most reference substances and uses relatively simple apparatus. In some instances, phase solubility techniques may permit recovery of highly purified crystals of the main component as well as a concentrated solution of the contaminating substances from which they may be isolated for identification by other methods. These fractions provide significant data bearing upon the acceptability of the reference substance. Phase solubility analysis is time-consuming and its execution demands painstaking attention to detail. It is therefore often regarded as unsuitable for routine use in control laboratories, but it has proved of great value in laboratories engaged in the assessment of reference substances. Some factors that may make the method inapplicable are degradation of the substance during the course of analysis, formation of a solid solution, and polymorphism in the main component. In the rare instance where the ratio of the impurity to the main component is the same as the ratio of their respective solubilities in the solvent system employed, the results may lead to erroneous interpretation.

3.3.1.2 *Differential scanning calorimetry.* Purity estimation by differential scanning calorimetry is based on the determination of the heat of fusion of the sample and the determination of the change in its melting point caused by the impurities present in it. This analytical method can be performed rapidly and is capable of high precision. It is, however, inapplicable if the substance melts with decomposition and this limits its value as a general procedure for purity estimation of reference substances. Like phase solubility analysis, it is also inapplicable where solid solutions are formed.

3.3.2 *Methods based on comparison with external standards and other methods*

3.3.2.1 *Chromatographic methods.* Methods of analysis based on chromatographic separation are especially useful for detecting and determining impurities in reference substances. Thin-layer chromatography and gas-liquid chromatography are often used, and high-

pressure liquid chromatography is finding increasing application. The individual components separated by chromatographic methods may sometimes be recovered for characterization.

Thin-layer chromatography employs apparatus that is simple and cheap, it is easy to carry out and is readily applicable even in the microgram range. It is frequently capable of separating closely related compounds, such as geometric isomers and the members of a homologous series. All the constituents of the chromatographed reference substance occur somewhere on the chromatogram. However, some constituents may remain on the starting line of the chromatogram, some may move with the solvent front, some may migrate at the same rate as the main component, and some may remain undetected. The usefulness of the method may be greatly enhanced by means of two-dimensional chromatography and by employing a number of different solvent systems and a variety of methods of detection. It is probably the most widely used method for assessing chemical reference substances. The method is, however, rarely applicable on a quantitative basis but has great value in tests devised to limit the concentration of the amounts of impurities. Variations that may be encountered in material used as stationary phases, particularly when they are obtained from different suppliers, may sometimes cause marked differences in the migration of substances in the thin-layer chromatogram.

The resolving power of gas-liquid chromatography and of high-pressure liquid chromatography usually exceeds that of thin-layer chromatography. Both the first two methods also have the advantage of being readily applicable on a quantitative basis, but require more complex equipment. The use of high-pressure liquid chromatography, employing a spectrophotometric method of detection, is of especial value in the examination of reference substances destined to be used in connexion with ultraviolet spectrophotometric assays. Gas-liquid chromatographic methods, on the other hand, are of particular value in detecting and determining volatile impurities, including solvent residues in reference substances.

3.3.2.2 *Spectrophotometric methods.* Ultraviolet spectrophotometry is a widely used method for determination of purity. Since it depends upon the presence of a characteristic chromophore, it is capable of detecting impurities that contribute excessively to the absorbance value and may indicate the presence of impurities that have negligible absorbance. However, the utility of the method is limited by the small number of absorption maxima in the ultraviolet range,

the large numbers of compounds containing similar characteristic chromophores, and the need for reliance on an external reference standard.

As previously noted, infrared spectrophotometry is of less value for detecting impurities. However, it is sometimes useful, for example in determining the proportion of the geometric isomers. Nuclear magnetic resonance spectroscopy is also useful occasionally for the determination of purity.

3.3.2.3 *Titrimetric methods.* Titrimetric methods provide a valuable means of confirming the identity and purity of a candidate reference substance and have the distinct advantage that they are usually stoichiometric in nature and that the external standard used may be chosen with regard to its suitability as a primary reference material.

3.3.2.4 *Optical rotation methods.* Many reference substances are optically active and the relative proportion of optical isomers is usually determined by an optical rotation method. The quantitative use of these techniques is well established and can yield results of high precision, depending on the solvent and the wavelength chosen for measurement.

3.3.2.5 *Other methods.* Other methods, such as gravimetric analysis, electrophoresis, atomic absorption spectroscopy, polarography, and combustion procedures, may be valuable in the determination of purity. Several of the foregoing methods, as well as other techniques, may be used to determine functional groups or elements. The concentration of impurity in the reference substance may then be calculated, using an assumed atomic or molecular weight for the impurity.

3.3.3 *General considerations*

Whatever methods are used to evaluate chemical reference substances, it is essential that an accurate assessment of the moisture content and the content of other volatile contaminants be made. This may often be achieved in total terms by drying, under defined conditions that are appropriate to the substance being examined. In certain cases, however, this may not be possible, in which case the water content may be determined by Karl Fischer titration and the content of volatile solvents by gas-liquid chromatography. Without an accurate assessment of these values at the time that other determinations are

being made, judgements as to the acceptability of the candidate material will be invalid.

4. HANDLING AND DISTRIBUTION OF REFERENCE SUBSTANCES

The measures employed in handling, distributing, and using established chemical reference substances must provide for assurance that their integrity will be safeguarded and maintained throughout their period of use.

4.1 Packing and storage

Containers for reference substances should afford protection from moisture, light, and oxygen. From the point of view of the stability of the substances, sealed glass ampoules are the best containers, but they suffer from certain disadvantages, notably the risk of contaminating the substance with glass particles when the ampoules are opened and the difficulty of re-closure. Sealed ampoules are therefore principally used for materials that must be kept in an oxygen-free atmosphere. Certain materials may require even more elaborate protection. Most chemical reference substances, however, are conveniently supplied in re-closable containers, which should be uniform in type and size to facilitate distribution. It is emphasized that the permeability of containers to moisture is an important factor in determining their suitability as containers for reference substances.

The packing of a batch of a reference substance into containers is a small-scale operation for which suitable equipment is not always available to the manufacturer of the substance. Therefore the packing of reference substances is usually undertaken by the authorities responsible for them.

Vibration spatulas and similar devices are available for dispensing substances on a small scale, but these should be used with caution because of the risk of segregation of particles of different size during the filling operation, which may lead to inhomogeneity. Screw-type feeders have also been constructed, but as yet are not commercially available, and so far the packing of reference substances has been done manually.

Several pharmaceutical reference substances have to be packed under nitrogen or in conditions of controlled humidity. The use of a glove-box is of great value in this connexion.

The various stages in packing reference substances should be controlled to avoid contamination of the sample, mislabelling of containers, and other factors that might result in an unsatisfactory reference substance.

Information about suitable storage conditions for reference substances can often be obtained from the manufacturer and should be requested routinely when a new reference substance is established. Theoretically the stability of the substances should be enhanced by keeping them at low temperatures but, for substances that contain water, storage below 0 °C may impair the stability. It should also be remembered that the relative humidity in normal refrigerators or cold-rooms may be high and, unless ampoules or other tightly closed containers are used, the intended improvement in stability by storage in such places may be more than offset by degradation due to the absorption of moisture. Storage at about +5 °C with precautions to prevent such absorption has proved satisfactory for most chemical reference substances.

4.2 Stability and periodic re-evaluation

It should be recognized that a reference substance is an integral part of the drug specification. Thus, if the reference substance deteriorates, this also implies a change in the specification of the drug. It is therefore of the utmost importance that the stability of reference substances should be monitored by regular re-examination and that replacement should be made as soon as a significant change in a property is noted.

The definition of what is a "significant change" differs, however, with the intended use of the reference substance. Degradation products in a substance amounting to several per cent may not impair the usefulness of the material in an infrared identification test. For reference substances that are used in chromatographic tests or in assays, however, even small amounts of impurities may be quite unacceptable. In the establishment of standards for reference substances, consideration must be given to the intended use of the substance and to the performance characteristics of the analytical methods for which it is to be used. It must be recognized, however, that the tolerable degree of degradation will be different from case to case.

Laboratories in charge of collections of reference standards should have a system for regular re-examination of the materials in stock. When sufficient experience has been gained, the frequency of retest-

ing may be modified. In this context, however, it is appropriate to bear in mind that the stability of a specially prepared reference substance may not always parallel that of commercial samples of the same material.

The selection of suitable analytical methods for monitoring the stability of reference substances depends on the nature of the substance. Thin-layer chromatography is used extensively and often simple tests, such as determination of water or pH, are useful for recognizing the onset of degradation.

When quantitative estimation of the degree of degradation is needed, more complicated techniques, such as phase solubility analysis, differential scanning calorimetry, or chromatography coupled with quantitative determination of the separated components, must be used.

Change in the moisture content of reference substances is a phenomenon that is difficult to control. To establish suitable conditions for packing operations and storage that might minimize such changes, it is recommended that, for each substance, data be obtained relating to moisture content and relative humidity.

4.3 Information to be supplied with reference substances

Some centres for reference materials supply extensive documentation with the reference substances, and include directions for use. Other centres supply no information except the name of the substance and of the issuing authority. Such differing practices may result in improper use of the reference substances. It is desirable that recommendations should be made concerning the information to be supplied with reference substances and its manner of expression.

Labels on chemical reference substances should give the following information:

- (a) name of the substance;
- (b) type of reference substance (e.g., International Chemical Reference Substance, or National Chemical Reference Substance, or Authentic Specimen);
- (c) name and address of the issuing authority;
- (d) approximate quantity of material in the container; and
- (e) batch or control number.

The following information should be given, as necessary, either on the labels or in associated documents:

- (i) recommended storage conditions (if special conditions apply, these should be given on the label);

- (ii) intended use of the reference substances;
- (iii) directions for use (e.g., instructions about drying the material before use and any necessary cautionary statements);
- (iv) information about the composition of the reference substance, which is needed for calculation of the results of tests in which the substance will be used; and
- (v) a disclaimer of responsibility when reference substances are misused, or stored under inappropriate conditions, or used for other purposes than those intended by the issuing authority.

It is recommended that the analytical data given in the certificates supplied with the reference substances should be restricted to what is necessary for the proper use of the substances in the tests and assays for which they are provided. The full analytical reports, should, however, be available when needed for evaluation of the suitability of the reference substances for uses other than those originally intended. It might also be desirable to give more general information about the reference substances concerned, either on separate leaflets or incorporated in the certificates.

4.4 Expiry of reference substances

The question of whether expiry dates should be assigned to reference substances is of great importance both to the users and to the distributors of the substances. The arguments against expiry dating are that it might lead to the unnecessary discarding of satisfactory materials and that considerable experimental work would first have to be carried out to make the setting of meaningful expiry dates possible.

If it is considered necessary to specify an expiry date in a particular case, the date should be stated on the label. At present, most reference substances are replaced by new batches only when this has been shown to be necessary by re-evaluation. This procedure minimizes unnecessary waste of valuable materials, but in order to make it completely satisfactory it would be necessary to devise effective means of informing analysts in possession of reference substances about any replacement of batches.

4.5 Distribution problems

Distribution of reference substances within a country usually presents no problems. However, when samples are to be sent to other countries, both the sender and the receiver of the goods may encounter difficulties because of the vagaries of postal and customs regulations.

At present, distributors of reference substances are wasting a considerable portion of their resources in seeking information concerning the different import regulations in various countries and in filling in the required forms. Means should be sought to reduce such difficulties and barriers to the effective distribution of reference substances.

5. REFERENCE MATERIALS CALIBRATED AGAINST INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

The establishment of reference materials that have been correlated with the International Chemical Reference Substances may be desirable for various practical reasons, e.g., the latter may not be available in adequate quantities to supply all local needs. Moreover, the availability of such reference materials (for example, on a regional basis) should result in a reduction of the time between ordering and receiving the materials.

The authority to establish a reference substance for national or regional use should be clearly defined by the appropriate drug regulatory body. If an International Chemical Reference Substance exists, it is desirable that all corresponding reference substances should be correlated with it in order to obviate the proliferation of possibly dissimilar reference substances. The first step in establishing such a derived material would be to form an estimate of the amount that might be needed for a period of perhaps three to five years (the duration of storage would depend on the known stability characteristics of the material in question), to define the intended use of the substance, and to determine the extent and nature of testing that is required to evaluate it.

Once the material has been obtained, its identity should first be verified (for example, by infrared spectrophotometry in comparison with the International Chemical Reference Substance) and it should be examined by an appropriate stability-indicating procedure so as to provide a starting point for routine stability monitoring. If the material is to be used as a quantitative assay standard, it and the International Chemical Reference Substance should be subjected to a collaborative test following a strictly defined protocol with the participation of at least three laboratories. From the results so obtained, a value for the content of the assayed component should be assigned. Additionally, the substance should be shown to comply with all the requirements of its specification and it should be confirmed that it is suitable for its intended use.

Once established, the material should be packed in an appropriate way (as nearly as possible in the same way as the corresponding International Chemical Reference Substance) and it should be regularly monitored, in comparison with the primary reference material, to confirm that unacceptable deterioration is not occurring.

6. MEANS OF PROMOTING EFFECTIVE EXCHANGE OF INFORMATION AND ENSURING COOPERATION BETWEEN ORGANIZATIONS ESTABLISHING REFERENCE SUBSTANCES

During the past few years, there has been an increasing exchange of information between laboratories concerned with the evaluation of reference substances. Cooperation that began on a personal and *ad hoc* basis is now, in some cases, being put on a more formal footing. There is a need, however, for circulating timely notifications of the work to be undertaken. In every instance, this should be done well before making any approach to a pharmaceutical manufacturer for the supply of material. In this way, it would be possible for a manufacturer to set aside a portion of a particular batch, so that sufficient of the proposed reference material would be available for all expected needs. The advantages of this procedure would be: first, that the studies carried out might be shared by collaborating laboratories; secondly, that the same reference material would be used by each issuing authority; thirdly, that if supplies of that material at one laboratory were depleted, appropriate arrangements might be made to share the remaining material from the other laboratories. Finally, there would be considerable benefit to industry since requests for the supply of reference materials would be coordinated and would be reduced in frequency.

In such a cooperative effort, it might also be possible for the manufacturer to pack the reference substance into appropriate standardized containers so that any variation due to storage and transport would be minimized.

From time to time, each laboratory will need to replace a certain number of reference substances. It would be advantageous for each laboratory to review its needs well in advance so as to permit a concerted request to be made to a manufacturer, thus achieving the benefits mentioned above.