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WHO Expert Committee on Specifications for Pharmaceutical Preparations

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Geneva, 2–6 December 1985

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirtieth report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 2 to 6 December 1985. The meeting was opened on behalf of the Director-General by Dr J.F. Dunne, Chief, Pharmaceuticals Unit, who reviewed the substantial support offered by the Committee in its previous reports to countries seeking to establish basic systems of quality control for imported and domestically produced pharmaceutical products. In its work of developing *The International Pharmacopoeia* and promoting the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce, one of the Committee's constant concerns was to encourage the rational use of drugs, as called for in Resolution WHA37.33 of the Thirty-seventh World Health Assembly and at the Conference of Experts on the Rational Use of Drugs held in Nairobi from 25 to 29 November 1985.

1. THE INTERNATIONAL PHARMACOPOEIA

1.1 Specifications for pharmaceutical substances

The Committee noted that with the publication of the third volume of the third edition of *The International Pharmacopoeia* in 1987, monographs will have been provided for almost all substances in the WHO Model List of Essential Drugs. The only exceptions are substances added to the Model List when it was last revised in December 1984. The monographs for these will be published as addenda once the necessary consultations with national drug regulatory authorities and pharmaceutical manufacturers have been completed and they have been formally adopted by the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

Efforts will be continued to replace the few remaining references to analytical procedures involving techniques that are beyond the

capacity of the model quality control laboratory described in the Committee's previous reports by tests in which classical methods of analysis are used. In doing this, every care will be taken to preclude any relaxation in standards of quality.

1.2 Specifications for dosage forms

If *The International Pharmacopoeia* is to respond fully to national needs, it must contain monographs on final dosage forms. General descriptions of dosage forms in conformity with the basic principles adopted in the Committee's twenty-seventh report and including definitions, physical requirements, and tests of performance for tablets, capsules, and parenteral preparations, will be included in the fourth volume of the third edition of *The International Pharmacopoeia*. In this connection the Committee makes the following recommendations:

1.2.1 *Uniformity of mass and content*

Solid dosage forms, including tablets, capsules, and preparations intended for reconstitution prior to parenteral administration, must conform in mass and content with the requirements in the monographs if reproducibility of clinical response is to be assured. Dosage units can easily be weighed in the simplest of laboratories, but quantitative determination of their chemical content is analytically demanding. The Committee therefore recommends that such analysis be considered only when the active drug substance accounts for 5% or less of the mass of the dosage form (i.e., only when the dosage form contains a relatively small quantity of a highly potent drug). This advice supersedes recommendations made in an earlier report.[1]

1.2.2 *Disintegration tests for tablets and capsules*

Disintegration of the dosage unit after ingestion is necessary for the release, dissolution, and consequent absorption of its active constituents. The process may be impaired, and bioavailability compromised, by basic errors in formulation or manufacture, including a lack of disintegrants, an excess of lubricants, or

[1] WHO Technical Report Series, No. 645, 1980.

overcompression. Improper or prolonged storage may have the same effect, owing, for instance, to the aging of coatings or the hardening of tablets. The formulation of tablets or capsules that can be relied upon to disintegrate appropriately *in vivo* can sometimes tax the ingenuity of a manufacturer faced with the need to create a product that is also stable, distinctive, and acceptable to the patient.

In the case of solid dosage forms containing active constituents that are readily soluble in the intestinal contents, demonstration of the process of disintegration under standardized conditions *in vitro* provides a valuable indicator of the ease of absorption *in vivo*. It also offers a useful and convenient parameter for assessing the consistency of performance between different batches of the same product.

Disintegration tests are simply and rapidly performed. The apparatus required is inexpensive and no auxiliary analytical equipment is needed since the endpoint is determined by visual inspection alone. The Committee therefore recommends that disintegration tests for tablets and capsules should always be laid down in *The International Pharmacopoeia,* unless the monograph calls for a dissolution test. However, since slight variations in the method used may readily influence the results obtained, the Committee recommends that the test to be included in *The International Pharmacopoeia* be modified in one important respect from those currently described elsewhere.

As the test is now generally performed, the dosage form is agitated in a liquid medium. It is contained in a tube with an open wire mesh at its lower end and is kept in apposition with that mesh by an unanchored perforated plastic disc placed above it. Products of disintegration are forced through the mesh into an outer chamber of the apparatus and the process is complete when there is no residue left sticking to the mesh. However, viscous substances, including natural gums and gelatin, may give rise to false negative results. The plastic disc is intended to make it possible to determine the endpoint more precisely. Unfortunately, by increasing turbulence in the liquid medium and by its percussive action it also accelerates the process of disintegration to such an extent that it is now recognized that products with diminished bioavailability may still conform to the test requirements.

The Committee therefore recommends that, for the purposes of *The International Pharmacopoeia,* discs should not be utilized in disintegration tests for tablets and capsules.

1.2.3 *Dissolution tests for tablets and capsules*

Dissolution tests were introduced to provide more precise information than is available from disintegration tests on the bioavailability of pharmaceutical products.

Several national drug regulatory authorities in highly developed countries now require not only dissolution testing but also direct evidence of bioequivalence as a precondition for licensing new formulations of established products. The cost of the studies involving human subjects that are needed to obtain data on bioavailability and bioequivalence is considerable. General adoption of this policy would consequently have profound implications for the marketing of generic products. It would also affect the purchase of drugs by open competitive tender and thus the current procurement policies of many developing countries. For this reason the Committee considers that it is important for WHO to obtain information on the extent to which such products are being rejected on grounds of inadequate dissolution or bioavailability and, if possible, on the types of product that are implicated.

On the basis of the considerable amount of information at present to hand the Committee considers that in many instances a correlation has been established between the *in vitro* dissolution characteristics of solid oral dosage forms of pharmaceutical products and their bioavailability as determined in human beings. It also recognizes, however, that although a marked trend toward dissolution testing is evident in the pharmacopoeias of the most technically advanced nations, its general adoption would not be practicable in many developing countries. The cost of the equipment is less than that of many key analytical instruments, but wide application of the tests would make unreasonable demands upon the time of trained analysts.

The Committee further proposes that, when these tests are considered necessary, their limits should be based not only on existing national pharmacopoeial standards but also — where feasible — on prospective examination of representative formulations of products currently available in many countries. It was suggested that a collaborative study be conducted for this purpose, involving national quality control laboratories from each of WHO's regions.

1.3 Sterility and sterilization

The Committee wishes to place on record that when a definition of sterility is worked out for *The International Pharmacopoeia* it should not be based on statistical norms. Instead, emphasis should be placed on the methods by which sterility is achieved and how they are validated. It is particularly concerned that a statement made in an earlier report of the WHO Expert Committee on Biological Standardization, applicable only to one particular aspect of the production of biological substances (validation of aseptic filling procedures) and setting a contamination rate limit of less than 0.3%, has been erroneously interpreted as setting a general criterion for sterility.

1.4 Particulate matter in parenteral preparations

Visual inspection of parenteral preparations for particulate matter can be performed virtually anywhere and by persons with a minimum of training. It is an important element both in quality control as practised by manufacturers, in which the objective should be the inspection of every unit, and in regulatory examination of finished products. The Committee therefore considers that this procedure should be included as a requirement for parenteral preparations in *The International Pharmacopoeia.*

Particulate matter too fine to be detected visually may still be large enough to occlude capillaries. Two methods of detecting and estimating the amounts of such particles in injectable preparations have been developed. One, based on filtration and microscopy, requires an exceptionally high level of technical competence and a particle-controlled working environment. The other, based on electronic measurement of scattered light, requires expensive equipment. The Committee considers that neither method is at present practicable in many smaller national laboratories and that they cannot therefore be recommended at the moment for inclusion in *The International Pharmacopoeia.* Importing agencies and regulatory authorities, however, are advised to request particle-controlled products.

1.5 Oral rehydration salts

Having regard to the prime importance of oral rehydration salts in developing countries and the large number of manufacturers engaged in their production, the Committee considers that priority should be given to drafting a suitable monograph for inclusion in *The International Pharmacopoeia*. In particular, valid acceptance limits for the various ingredients need to be established in the light of clinical as well as pharmaceutical considerations.

1.6 Packaging materials

Drug products need to be protected against contamination and degradation due to external factors. They consequently need to be packaged in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. The Committee acknowledges the valuable contribution of several industrial laboratories to the development of appropriate testing procedures. However, the limits of acceptability in these various respects depend, at least in part, on climatic variables. Recommendations in *The International Pharmacopoeia* can only be advisory; precise quantitative standards will have to be locally determined.

In this connection the Committee wishes to draw attention to the authoritative, generally applicable guidelines on packaging processes and materials, intended to supplement basic standards of good manufacturing practices, which have recently been issued by the Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products.

2. GOOD LABORATORY PRACTICES IN GOVERNMENTAL DRUG CONTROL LABORATORIES

In Annex 1 of its twenty-ninth report the Committee presented recommendations on the staffing and organization of two model national laboratories for drug surveillance and control, having particular regard to needs in developing countries where no such facilities yet exist. The tests and assays undertaken in these laboratories to establish whether a pharmaceutical product

conforms to the quality specifications claimed for it must meet exacting standards, since the results provide a basis for administrative decisions relating to the product and, where necessary, for legal action.

The required accuracy can be achieved only if management is effective and meticulous operational procedures are instituted and maintained; guidelines on "Good Laboratory Practices in Governmental Drug Control Laboratories", intended to meet these needs, are set out in Annex 1. The scope of these guidelines ranges from matters of organizational structure and staffing to advice on routines and management, documentation requirements, and the evaluation of test results. The sections on analytical work are primarily concerned with the performance of chemical and physicochemical analyses rather than with microbiological, pharmacological, or other specialized test methods. They are not fully applicable to quality control laboratories in manufacturing establishments, where test procedures and documentation requirements may be different.

The guidelines are intended to be illustrative rather than prescriptive and will need to be adapted to differing local circumstances and particularly to the size of the laboratory. Alternative approaches to management are acceptable provided that reliability of operation remains assured. In small laboratories many of the responsibilities defined will lie with one qualified analyst, but the principles of management and procedure will still be the same.

Any judgement concerning the quality of a product depends on adequate sampling as well as on correct test procedures. It is the responsibility of the manufacturer, in establishing sampling and test protocols, to demonstrate with an acceptable degree of certainty that any sample taken at random from a given batch will meet pharmacopoeial requirements. The standards of *The International Pharmacopoeia* are intended to apply to any available sample at any time during its shelf-life. An article is considered to be of pharmacopoeial quality if any sample of the size stipulated in the monograph meets requirements at any time during storage, distribution, or use. Compliance with the monograph requires compliance with every test.

It is suggested that WHO should give further consideration to the preparation of guidelines on the principles and statistical basis of sampling procedures required during manufacture, with particular attention to the needs of small local manufacturers.

3. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

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

3.1 Establishment of reference substances

Since the Expert Committee last met, in December 1983, 12 new International Chemical Reference Substances have been established and depletion of stocks has made it necessary to introduce replacement batches of 5 already established substances. The total collection now comprises 124 International Chemical Reference Substances and 13 Melting-Point Reference Substances (Annex 2).

To support all the specifications contained in volumes 2 and 3 of the third edition of *The International Pharmacopoeia* a further 54 new reference substances will be needed. Analytical examination of 9 of these substances is nearing completion. However, because of limited resources and the need to introduce replacement batches for stocks that are now largely depleted, work on the remaining substances is unlikely to be completed in under 3 years.

It has therefore been agreed that the Collaborating Centre should establish replacement batches for existing International Chemical Reference Substances only if that substance is to be included in the third edition of *The International Pharmacopoeia*.

The Committee further agrees that if the continued supply of International Chemical Reference Substances is to be assured, unnecessarily rapid depletion of stocks must be avoided. Many laboratories need further advice on the correct and efficient use of the various classes of reference materials, and detailed guidelines are required on the establishment of secondary reference materials, having regard to experience obtained in various existing national and regional programmes.

3.2 National and regional reference substances

The Collaborating Centre has continued to give advice to various agencies that are establishing national or regional reference substances for use as working standards. While the Committee

[1] WHO Collaborating Centre for Chemical Reference Substances. *Report on the work in 1983* (unpublished document WHO/PHARM/84.513); *Report on the work in 1984* (unpublished document WHO/PHARM/85.517).

recognizes the need for establishing such collections, it cautions that the reference substances concerned must be very carefully calibrated against the International Chemical Reference Substances or other primary reference materials if reliable, internationally effective standards of quality in pharmaceutical substances are to be maintained.

3.3 Considerations for the future

The Committee expresses its appreciation to the Collaborating Centre and its staff for the work accomplished and fully endorses the approaches now being adopted. It also requests that its grateful acknowledgement be conveyed to the National Corporation of Swedish Pharmacies for the considerable contribution it has made over many years, both in resources and funding, to enable the WHO Chemical Reference Substances programme to be sustained.

The Committee recognizes that every possibility must be explored of reducing the now unacceptably high budgetary deficit of the Collaborating Centre and urges WHO to examine any possible way of obtaining support. Whereas one obvious possibility is to levy a charge on materials supplied to governmental drug control laboratories, it is vital to ensure that laboratories in developing countries lacking convertible currencies are not deprived of essential reference materials. If that were to happen, present plans to develop systems of quality assurance in countries already very vulnerable to substandard and spurious products would be seriously jeopardized.

A significant reduction in costs and labour could certainly be achieved in instances in which they are used solely to verify identity if reference substances were replaced by infrared reference spectra. The present heavy workload of the Collaborating Centre could be reduced still further if other national laboratories, now experienced in establishing regional or national reference substances, were able to contribute to the establishment of International Chemical Reference Substances.

The World Health Organization already provides national authorities with valuable assistance by informing them of appropriate industrial sources of bulk materials suitable for establishing as regional reference substances and by coordinating supplies when joint needs arise and there is a possibility of sharing the work of validation between two or more countries.

4. INTERNATIONAL INFRARED REFERENCE SPECTRA

The need to develop standard infrared reference spectra to supersede those international chemical reference substances used solely to verify the identity of pharmaceutical substances is explained at length in the twenty-seventh report of the Committee. A pilot project to develop methods of producing and validating these spectra is now in operation.

Spectra are recorded by the Pharmaceutical Institute, Federal Institute of Technology, Zurich, Switzerland, on a medium-resolution infrared spectrophotometer linked to a computerized data storage and retrieval system. All spectra are retrievable in their original form from this system, together with a print-out indicating the wave number and intensity of each peak and also the method of pretreatment of the sample from which it was derived. All spectra are derived from materials authenticated by WHO and will be subjected to a validation procedure that will involve several national drug quality control laboratories in both developed and developing countries. The results will be reviewed at the end of 1986 to determine the feasibility of making the project fully operational.

Should the system become operational, validated spectra will be distributed on request to national drug quality control laboratories from the WHO Collaborating Centre for International Chemical Reference Substances, Stockholm, Sweden, and methods for using them in routine analyses will be worked out.

5. TRAINING PROGRAMME IN DRUG ANALYSIS

General guidance on the group training of recent science and pharmacy graduates in drug quality control was given in the twenty-ninth report of the Committee. Annex 3 of the present report sets out a detailed model syllabus for such courses, which could be organized in many national quality control laboratories. It covers both the practical and the theoretical aspects of drug analysis for regulatory purposes.

A prime objective is to teach the students how to work efficiently and how to determine priorities for analyses so that limited resources can be used to best effect. This need is obviously most acute where facilities are most limited.

The syllabus provides for a general introduction to the objectives and principles of drug control and laboratory management,

followed by separate parallel courses in chemical, microbiological, and biological techniques of analysis. A 6-month course is proposed for both chemical and microbiological analysis, and a 3–4-month course for biological (pharmacological) techniques.

The sequence in which the subjects are listed is that in which the various analytical techniques are used in the control of specific categories of pharmaceutical raw materials and dosage forms, and it differs in this respect from the usual presentation of analytical methods.

Obviously trainees working in a first-stage laboratory, such as that described in Annex 1 of the twenty-ninth report of the Committee, will not need practical experience in all the methods of analysis covered by the syllabus. If the training is to be used to best advantage, it is therefore important for the course organizer to obtain advance information on the facilities available to participants in their own countries.

The Committee further recommended that a simpler syllabus should also be drawn up for the training of laboratory technicians and that courses should be organized for laboratory managers.

The Committee noted with appreciation that with the help of funds from both government sources and nongovernmental organizations, including the Commonwealth Pharmaceutical Association, the International Federation of Pharmaceutical Manufacturers Associations and the World Federation of Proprietary Medicine Manufacturers, well over 100 analysts from developing countries had already received individual or group training in quality control in the past few years. Courses are now also being arranged in drug inspection, in-process quality control, and the implementation of good manufacturing practice.

6. BASIC TESTS

The Committee wishes to express its appreciation to the many laboratories and individuals who have contributed to the development and verification of the basic (or simplified) tests for confirming the identity of more than 300 chemical entities, including virtually all those in the WHO Model List of Essential Drugs. These tests form the basis of a compendium published by WHO in 1986.[1]

[1] *Basic tests for pharmaceutical substances.* Geneva, World Health Organization, 1986, 205pp.

The Committee sees a need for a similar compendium of tests for dosage forms and endorses the work that WHO has already accomplished in this connection.

7. COUNTERFEIT PRODUCTS

The Committee noted the concern expressed during the WHO Conference of Experts on the Rational Use of Drugs held in Nairobi from 25 to 29 November 1985 regarding the extent to which counterfeit pharmaceutical products are in circulation, particularly in some developing countries. This concern was endorsed by one committee member who had recently obtained direct evidence of counterfeiting and smuggling practices in which articles containing no pharmacologically active ingredient were wilfully misrepresented as life-saving drugs.

The Committee wishes to emphasize that any such suspicion can readily be confirmed by using the basic tests for verifying the identity of pharmaceutical substances and that this precaution, together with better internationally organized information on the extent of these practices, would do much to reduce their frequency.

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Annex 1

GOOD LABORATORY PRACTICES IN GOVERNMENTAL DRUG CONTROL LABORATORIES

1. GENERAL

A governmental drug control laboratory is a laboratory maintained by the drug regulatory authority for carrying out the tests and assays required to establish that a drug conforms to the quality specifications claimed for it. Some countries maintain larger establishments described as "drug control centres" or "drug control institutes".

The contribution of a drug control laboratory to a national drug control system was described in the twenty-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (*1*). In most countries the laboratory is responsible for analytical services only, and not for pharmaceutical inspection. However, some aspects of inspection are considered in these guidelines.

A control laboratory can provide effective support for a drug regulatory agency and its inspection services only if the analytical results it provides can be relied upon to describe accurately the properties of the samples it assesses, to permit the correct

conclusions to be drawn about the quality of each drug, and to serve as an adequate basis for any subsequent administrative and legal action.

Correct assessment of the quality of a drug sample is dependent on:

—the submission of a representative sample to the laboratory, together with a precise indication of why the test is requested;
—a correctly planned and meticulously executed analysis; and
—a competent evaluation of the results to determine whether the sample complies with the specification.

Precise documentation and efficient routines are required to make each operation as simple and as foolproof as possible.

These guidelines provide advice on the analysis both of dosage forms and of pharmaceutical raw materials; particular consideration is given to developing countries wishing to establish governmental drug control laboratories or having recently done so.

Many of the recommendations are also relevant to drug testing in pharmaceutical production plants, but this is a matter of the repetitive testing of a limited number of pharmaceutical products, whereas governmental control laboratories theoretically have to deal with all drugs on the market and therefore have to use a wider variety of test methods.

2. MANAGEMENT AND OPERATIONAL ISSUES

2.1 Organizational structure

The full analysis of a drug sample involves a variety of different tests. In a small laboratory where relatively few analyses are undertaken a single analyst may have to take responsibility for carrying out all the chemical and physicochemical tests and evaluating the results. In large laboratories, on the other hand, the sample may be subdivided between several specialized subunits, each of which carries out the part of the analysis that calls for the particular skills and technology that it possesses. In every case, however, a "lead unit" or focal point must be made responsible for distributing and testing the sample and collating and interpreting the results.

The division of the laboratory into subunits may be based on the main techniques used (e.g., chemical unit, instrumental unit,

microbiological unit, unit for biological safety testing) or on the type of product tested (e.g., antibiotics unit, crude drug unit, radiopharmaceuticals unit). Whichever plan is chosen, care must be taken to ensure an even distribution of the workload between units and the precise allocation of responsibilities, particularly in the designation of lead units for particular types of drugs. Units specializing in single assay techniques, such as sterility testing, pyrogen testing or special physical measurements, should be regarded as collaborating units that perform specific tests at the request of the lead unit.

Division of a laboratory into subunits should never be allowed to inhibit communication between the staff involved in testing the same sample. Intercommunication helps the lead unit to piece together all the information on which the quality of the sample is ultimately judged.

Large laboratories need various supporting and coordinating sections, including a central registry and a specifications repertory. The size of these units will depend on the number of samples received and the number of different drugs subjected to testing. The head of the central registry must be a person with wide experience in analysis and will be responsible for receiving all incoming samples and accompanying documents, supervising their delivery to the lead units and keeping a constant check on the progress of analyses and the despatch of completed reports. He or she may also be required to collate and evaluate the test results for each analysis. The specifications repertory section maintains an up-to-date collection of all quality specifications and related documents.

2.2 Staffing

The head of the laboratory, and the heads of the various subunits in larger establishments, should be of high professional standing and have had extensive previous experience in drug analysis and laboratory management in a quality control laboratory in the regulatory sector or in industry. Non-supervisory analysts should be graduates in pharmacy, analytical chemistry, microbiology, or other relevant subjects. Technical staff should preferably hold diplomas in their subjects from technical or vocational schools.

The head of the laboratory must be satisfied that all key members of the laboratory staff have the requisite competence and are given grades matching their responsibilities. To encourage them in

carrying out their tasks, all staff should be made aware of the important contribution of drug control to public health. In many countries, national regulations prohibit staff from holding independent posts or consultant assignments.

To reduce the possibility of human error, supervisors should periodically arrange for standard samples to be analysed and, where called for, review the adequacy of existing staffing, management, and training procedures. Error is most likely to occur during non-instrumental operations, and particularly in preparatory work, from carelessness, fatigue, boredom, inadequate training or, sometimes, as a result of staff being given work beyond their level of competence. "Self-checking" procedures should be devised for instrument operators. Regular in-service training programmes should be arranged to update and extend the skills of both professionals and technicians. This not only keeps staff abreast of advances in analytical methods and instrumentation, but also provides opportunities for career development and promotion.

In large laboratories the staffing of the various units should be based not only on their workloads but also on the technical demands of the work involved. In most instances the ratio of technicians to analysts should be 1:3 in a chemical or physicochemical unit, and 2:5 in a biological or microbiological laboratory. The greater the proportion of routine analyses undertaken on products that, *a priori,* are not expected to be substandard, the greater the proportion of technicians that can be effectively employed. Non-routine work, and particularly the review of test methods for newly registered drugs, requires a higher proportion of fully qualified analysts.

2.3 Incoming samples

As an initial step in quality evaluation, each incoming sample and the accompanying documents should be numbered and logged in a central register, which may be a record book, a card file, or data processing equipment. The entry should indicate the date when the sample was received and the lead unit to which it was forwarded. To facilitate the routing and tracing of samples, a list of the lead units assigned to each drug on the market should be kept in the central registry. Any unlisted products can then be assigned on a case-to-case basis by the head of the laboratory.

All persons, and particularly pharmaceutical inspectors, who frequently submit samples should be provided with standard "test

request" forms and such a form should accompany each sample submitted to the laboratory. It should provide the following information:

—the name of the institution or inspector that supplied the sample;
—the source of the material;
—a full description of the product, including its composition, brand name, dosage form, concentration or strength, manufacturer, and batch number (if available);
—the size of the sample, and the reason for requesting the analysis.

Other information that is often needed includes the date on which the sample was collected, the size of the consignment from which it was taken, the expiry date, and the pharmacopoeial specification to be used for testing.

When the sample is first received it should be immediately inspected to ensure that the labelling is in conformity with the information contained in the test request. If discrepancies are found, or if the sample is obviously damaged, the fact should be recorded at once on the test request form.

No sample should be examined until the relevant test request has been received. If this is lacking, the sample should be safely stored until all the relevant documentation has been received. In emergencies a request for analysis may be accepted verbally. In this event all details should immediately be placed on record pending the receipt of written confirmation.

Incoming samples and test requests should be numbered consecutively. For each sample a self-adhesive label bearing this registration number should be affixed to the container in such a way as not to obliterate other markings of inscriptions. If a request refers to two or more drugs, to different dosage forms, or to different batches of the same drug, separate registration numbers should be assigned to each. Photocopies of all documentation should accompany each numbered sample when it is forwarded to the lead unit.

2.4 Analytical worksheet

A printed analytical worksheet with space for the following information should be used by the analyst to confirm that the sample has been examined in accordance with the requirements and, when necessary, to provide documentary evidence to support regulatory action:

—the registration number of the sample;
—the date of the test request;
—a description of the sample received;
—the quality specifications to which the sample was tested (including any additional or special methods employed);
—the results obtained, including any calculations necessary;
—the interpretation of the results and final conclusions.

Additional space should be provided to indicate whether and when portions of the sample were forwarded to other units for special tests (e.g., sterility, infrared spectrum), and the date when the results were received. To ease the flow of information between collaborating units a further set of printed forms can be useful. These can be sent out in duplicate from the lead unit with the sample to which they refer. In due course one copy is returned to the lead unit for attachment to the analytical worksheet, while the other is retained in the unit that undertook the work.

A separate analytical worksheet should be completed for each numbered sample. Each completed worksheet should be signed by the analyst responsible, initialled by the supervisor and placed on file for safe-keeping together with any attachments, including calculations and tracings of instrumental analyses. If this information is filed centrally in a registry, a copy of the worksheet should be retained in the lead unit for ease of reference.

It is still the custom in many laboratories for each analyst to keep a complete record of his work in a bound laboratory notebook with numbered pages. Although this has value it is an inconvenient form of documentation in a modern laboratory where results obtained on recording instruments or printed calculations have to be entered into the worksheet. If such a notebook is kept, it should be regarded as a supporting record only.

On the day the sample is received in the unit, the registration number, the date, the name of the product, and a description of the material received should be entered on the analytical worksheet. The

information contained in the test request should be checked against the data on the label and the findings recorded, dated, and initialled. Any discrepancies in the documentation, or between the data provided and the appearance of the sample, should also be recorded. Any queries should immediately be referred back to the provider of the sample.

The analyst must then determine what specification is to be used to assess the sample. In many cases, the test request will specify a particular pharmacopoeial monograph or manufacturer's specification and the analyst must find out whether the current version is available. If no precise instructions are given, the specification in the officially recognized national pharmacopoeia should be used or, failing that, the manufacturer's officially approved or other nationally recognized specification. The reference number of the specification should be entered on the worksheet and a photocopy of the document attached.

If no formally approved specification exists, preference should be given to a current monograph in a foreign pharmacopoeia. If no suitable pharmacopoeial monograph can be found, the requirements should be drafted in the laboratory itself on the basis of published information and any other relevant documentation (*1, 2*). Otherwise, if the general policy of the laboratory permits, the specification contained in the product licence may be requested from the manufacturer. Whatever happens, detailed notes on the specification selected and the methods of assessment used must be entered in the worksheet.

2.5 Testing

If specific tests such as sterility tests, pyrogen tests, or special physicochemical tests need to be carried out by another unit or by a specialized external laboratory, the analyst should prepare the request and arrange for the transfer of the required number of units (bottles, vials, tablets) from the sample. Each of these units should bear the correct registration number.

Testing should be started as soon as possible after the preliminary procedures have been completed. If this is not feasible, the reasons should be noted in the worksheet and the sample placed in a special locked storage cabinet.

Detailed guidance on test methods are contained in the general notices and monographs of official pharmacopoeias. The

following principles therefore apply only when no pharmacopoeial requirements are available or when ambiguous results are obtained.

Provided the result is unequivocally positive and the analyst is well acquainted with the technique, replicate chemical and physicochemical tests are not, in general, required for identity tests based upon colour reactions, precipitation tests, infrared spectra, ultraviolet identification, or thin-layer chromatography, nor are they required for purity tests based on the matching of colour or opacity against standards or on thin-layer chromatography. In some laboratories, however, purity tests are routinely run in duplicate as a check against accidental contamination. Assays to assess strength or level of impurity should always be replicated, however, whether they are based on titrimetry, gravimetry, colorimetry, ultraviolet measurements, gas-liquid chromatography, or high performance liquid chromatography. Replicate measurements should also be made of physical properties such as pH values, optical rotations, refractive indices, and melting temperatures. Whenever replicate measurements are made, the results should be recorded as the arithmetic mean of the estimates.

In other cases, the required number of replicate measurements is defined in the description of the method. This applies to physicochemical tests involving gas-liquid chromatography or high performance liquid chromatography and to biological assays whose results require statistical evaluation.

Whenever ambiguous results are obtained, or when the discrepancies between replicate measurements fall outside acceptable limits, at least two further replicate tests should be run, preferably by a different analyst. Any important discrepancies must be investigated. Aberrant results can be rejected only when they are clearly due to error. Otherwise, the mean values obtained by each analyst should be quoted separately to provide clear confirmation that the sample failed the test.

Errors arise not only because of human failings but also as a result of unsuitable or deteriorated reagents and chemical reference substances, inadequate instrumentation, inappropriate methods (particularly methods that are difficult to reproduce), and variations in the laboratory environment. Comparative estimations on standard samples can frequently help to detect such errors, particularly in cases in which the analyst lacks experience in the method he has used.

All values obtained in each test, including blank results, should immediately be entered on the worksheet, and all graphical data, whether obtained from recording instruments or hand-plotted, should be attached.

2.6 Evaluation of test results

The analyst should review the results as soon as possible after all the tests have been completed to determine whether they are mutually consistent and whether they meet the specification. All conclusions should be entered on the worksheet by the analyst and initialled by the supervisor.

The certificate of analysis issued by the laboratory should be based on the analytical worksheet. It should specify the sample and the registration number, state the specification to which the sample was tested, list and provide the results of all the tests that were performed and state whether or not the sample was found to comply with the requirements. Certificates stating that a sample is not in compliance with the required specification must always be signed by the head of the laboratory.

A sample may be recorded on the worksheet as conforming to specification only if it meets all the relevant requirements. Any discrepancy confirmed by replicate testing should be evaluated in relation to the results of the other tests and the conclusions reached should be discussed with the head of the laboratory before they are entered on the worksheet. This record should then be signed by each of the analysts involved.

In large laboratories responsibility for certifying samples that conform to specification usually lies with the lead unit. However, in the event of non-compliance, the head of the laboratory is ultimately responsible for recommending any regulatory action that is required.

2.7 Retention samples

A retention sample originating from the same consignment as the analytical sample must always be kept in the laboratory — when possible in the original container — for use if the results of the analysis are disputed. This is usually prepared by the lead unit from the sample as received. The sample should therefore be large enough to provide an adequate reserve even when a number of replicate tests are required.

Sometimes, however, the retention sample is prepared by the sampling inspector when the analytical sample is taken. In this case the two samples should be separately packaged and transferred together to the laboratory. The retention sample is then labelled as such and given a registration number before it is forwarded with the analytical sample for storage in the lead unit.

Once all the required tests have been performed, any remaining portions of the sample should be resealed in their original containers. They should then be labelled with the date on which they may be discarded and placed in a locked cabinet in central store, if necessary at low temperature. Samples found to comply with specification should be kept for at least 6 months. Those that do not should be kept for at least one year, or for any longer period specified in current regulations.

2.8 Specifications repertory

Every drug control laboratory must possess the current versions of all the specifications that it needs, whether they are contained in pharmacopoeial compendia or in manufacturers' registration documents. In a large laboratory the specifications repertory is a documentation service with responsibility for updating all the pharmacopoeias — including supplements, addenda, and corrections — used in the laboratory and maintaining a specifications file for all drugs marketed within the country.

The repertory should retain a list of all pharmacopoeias in the laboratory and ensure that adequate numbers of supplements and addenda are ordered. All updatings and corrections should be noted in the principal volumes to prevent obsolete sections being used. Additional or replacement pages for loose-leaf publications should be inserted immediately they are received; pages no longer valid should be removed.

In addition, every laboratory should maintain a file of non-pharmacopoeial quality specifications for drugs tested to specifications established either by the manufacturer or by the laboratory itself. The range of monographs in this file will depend on current legal requirements and on whether or not a published national or regional pharmacopoeia is accorded official status within the country. Each entry should be numbered and dated so that the latest revision can easily be seen. The copy in the repertory file should bear the date of approval by the national registration

authority or the lead unit and any other information relevant to the status of the monograph. All subsequent corrections or changes should be entered in these copies and endorsed with the date and the initials of the person making the entry. The master copy should never be released from the repertory; for laboratory use photocopies should be taken.

Manufacturer's specifications are the property of the company and in some countries are made available to governments strictly for registration purposes. In this case the quality control laboratory may need to negotiate their release with manufacturers or even, in some cases, to develop independent specifications. In other countries national laboratories are routinely asked to give their opinion on the specifications for each newly introduced product when it is registered by the drug regulatory authority.

2.9 Reagents

All reagents, including solvents, used in tests and assays must be of appropriate quality. They should be purchased from reputable manufacturers or dealers, preferably in small factory-filled containers suitable for laboratory use. Stocks stored in greater bulk are more vulnerable to contamination and degradation. Appropriate safety regulations should be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used. Those subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked as "Poison" and kept separately from other reagents in locked cabinets. A register of these substances must be maintained by the responsible member of staff. The head of each unit must accept personal responsibility for the safe-keeping of any of these reagents kept in the workplace.

Reagents made up in the laboratory should be prepared according to prescribed procedures and, when applicable, to published pharmacopoeial or other standards. Each label should clearly specify the contents, the manufacturer, the date received, and, as appropriate, the concentration, standardization factor, shelf-life, and storage conditions. Volumetric solutions made up by dilution should be labelled with the name of the manufacturer of the concentrate, the date of preparation, and the initials of the responsible technician.

Responsibility for making up reagents in the laboratory should be clearly assigned. Standardization of procedures is more readily implemented when this work is supervised by one person, even when the same reagents are used in several units. However, the reagents should not be moved unnecessarily from unit to unit and should be transported, whenever possible, in their original containers. When they are subdivided, they should always be transferred into scrupulously clean, fully labelled containers.

Whatever routine precautions are taken to ensure the adequacy of volumetric solutions, they should be checked whenever they are used in a test which indicates that a sample is not in compliance with specifications and the results of the check should be attached to the analytical worksheet.

Distilled water and deionized water should also be regarded as reagents and precautions should be taken to avoid contamination during their supply and distribution. Stocks should be checked at least once a month to ensure that they meet quality requirements: the specific conductance at 20 °C should not be greater than 2.0×10^{-6} $ohm^{-1}cm^{-1}$ and the chloride ion content should meet current pharmacopoeial requirements for purified water.

All reagent containers should be inspected to ensure that seals are intact both when they are delivered to the reagent store and when they are distributed to the units. These inspections should be recorded by initialling and dating the labels. Reagents that appear to have been tampered with should be rejected except in rare instances when their identity and purity can be confirmed by testing. Maintaining stocks of reagents in a central store promotes safety and continuity of supplies, particularly for substances that need to be ordered long in advance of delivery.

In a large laboratory the storage area should provide separate rooms for flammable substances, for fuming acids, including concentrated hydrochloric acid, nitric acid, and bromine, and for ammonia and volatile amines. Self-igniting materials, such as metallic sodium and potassium, should also be stored separately. All storage areas should be located and equipped in accordance with fire regulations. To promote safety and to reduce contamination of the laboratory environment, these reagents should never be stored elsewhere in the laboratory without good reason.

The store should be kept stocked up with the clean bottles, vials, spoons, funnels, and self-adhesive labels required for dispensing reagents from larger to smaller containers. Special equipment may

be needed for the transfer of larger volumes of corrosive liquids. The storekeeper should be trained to handle chemicals with the necessary care and safety.

2.10 Reference materials

Details of all the reference materials required should be kept in a central register. In a large laboratory this responsibility should be assigned to a specific person designated as the reference material coordinator. A national drug control laboratory that is required to establish reference materials for other institutions or for drug manufacturers will need to create a separate reference materials unit which will assume all the duties of the coordinator.

The register should contain details not only of all official reference substances and reference preparations, but also of secondary reference materials and non-official materials prepared in the laboratory as working standards. Each entry should be assigned a number and should give a precise description of the material, its source, the date of receipt, the batch designation or other identifying code, the intended use of the material (infrared reference material, impurity reference material for thin-layer chromatography, etc.), the place in the laboratory where it is stored, and any special storage conditions.

In addition to the register, a file should be kept containing full information on the properties of each reference material. In the case of working standards prepared in the laboratory the file should include the results of all tests and checks used to establish the standard and the initials of the responsible analyst.

Its laboratory identification number should be marked on each vial of the material and this must be quoted in the analytical worksheet every time it is used. A new number should be assigned to each new batch of material as soon as it is delivered or prepared. All reference materials should be inspected at regular intervals to make sure that they have not deteriorated and that they are being stored under appropriate conditions.

Further guidance on establishing, handling, and storing reference materials is contained in Annex 1 of the twenty-eighth report of this Committee (*3*).

2.11 Instruments and their calibration

Instruments are subject to wear, corrosion, and mishandling. If they are not in good working order they may give rise to serious analytical errors that may remain undetected unless systematic checks are made.

Whenever possible, regular servicing of instruments by specialist maintenance teams should be arranged. Instruments exposed to high levels of humidity should be resistant to corrosion and adequately protected against mould and fungal growth. Where line voltage is variable, suitable voltage stabilizers should be installed.

Some instruments may need to be protected from extremes of humidity or temperature in a specially designed area. Otherwise, analytical instruments can be either grouped together or dispersed between the various units. The choice will depend on the types of instruments, their fragility, the extent to which they are used, and the skills required to operate them.

Regular calibration of all instruments used to measure the physical properties of substances is essential and specific schedules should be established for each type of instrument, having regard to the extent to which it is used. pH meters should be calibrated at least once a day. The reliability of the wavelength scale of melting-point instruments and spectrophotometers operating in the ultraviolet region should be checked once a week and a full calibration undertaken once a month. Infrared spectrophotometers require calibration every quarter, while refractometers and spectrofluorometers should be serviced half-yearly. Analytical balances should also be serviced at least half-yearly by a qualified balance specialist.

Volume 1 of the third edition of *The International Pharmacopoeia* describes the procedure for calibrating refractometers, thermometers used for the determination of melting temperature, and potentiometers for pH determination (*4*). It also explains the methods for checking the reliability of the scales on ultraviolet and infrared spectrophotometers and spectrofluorometers. A clear description of the standard operating procedure should be placed beside each instrument together with a schedule of the dates on which it is due for calibration.

Whatever routine precautions are taken to ensure the calibration of instruments, they should also be checked whenever they are used in a test which indicates that a sample is not in compliance with

specification. The results of the check should be attached to the analytical worksheet.

2.12 Safety in drug control laboratories

Safety depends on the maintenance of exemplary technical standards and laboratory discipline. Safety instructions, both general and specific, should be given to each new member of staff and should be regularly supplemented with written material, poster displays, audio-visual material, and occasional seminars.

General rules for safe working include:

(1) prohibition of smoking, eating, and drinking in the laboratory;
(2) familiarity with the use of fire-fighting equipment, including fire extinguishers, fire blankets, and gas masks;
(3) use of laboratory coats or other protective clothing;
(4) adequate insulation and spark-proofing of electrical wiring and equipment, including refrigerators;
(5) full labelling of all containers of chemicals, including prominent warnings (e.g., "Poison", "Flammable") whenever appropriate;
(6) observation of safety rules in handling cylinders of compressed gases and familiarity with their colour identification codes;
(7) avoidance of solitary work in the laboratory;
(8) provision of first-aid materials and instruction in first-aid techniques, emergency care, and use of antidotes.

Protective clothing should be available, including goggles, masks, and gloves. Rubber suction bulbs should be used on all pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents, and solvents, and particularly in the use of safety containers or baskets to avoid spillage from containers. They should also be warned of the danger of violent, uncontrollable or dangerous reactions when mixing specific reagents. They must be instructed in the precautions required when, for example, mixing water and acids, acetone-chloroform and ammonia, or flammable products and oxidizing agents, and they should avoid the use of peroxidized solvents. They must also be instructed in the safe disposal of unwanted corrosive or dangerous products by neutralization or

deactivation and of the need for safe and complete disposal of mercury and its salts.

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

REFERENCES

1. WHO Technical Report Series, No. 645, 1980, Annex 2.
2. WHO Technical Report Series, No. 614, 1977, Annex 1.
3. WHO Technical Report Series, No. 681, 1982, Annex 1.
4. *The International Pharmacopoeia,* third edition, volume 1: *General methods of analysis.* Geneva, World Health Organization, 1979.

Annex 2

LIST OF AVAILABLE INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

January 1986

General information

International Chemical Reference Substances are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The International Pharmacopoeia* or proposed in draft monographs.

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 the use of these substances.

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 from the Centre and may be obtained on request.

Ordering information

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

WHO Collaborating Centre for Chemical Reference Substances
Apoteksbolaget AB
Centrallaboratoriet
S-105 14 Stockholm
Sweden
(Telex: 115 53 APOBOL S)

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

Reference substance	*Package size*
aceclidine salicylate	100 mg
p-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
atropine sulfate	100 mg
azathioprine	100 mg
bendazol hydrochloride	100 mg
benzobarbital	100 mg
benzylamine sulfate	100 mg
benzylpenicillin potassium	200 mg
benzylpenicillin sodium	200 mg
bephenium hydroxynaphthoate	100 mg
betamethasone	100 mg
betanidine sulfate	100 mg
bupivacaine hydrochloride	100 mg
caffeine	100 mg
carbenicillin monosodium	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
chlortalidone	100 mg
cloxacillin sodium	200 mg
cortisone acetate	100 mg

Reference substance	*Package size*
dapsone	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
NN'-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
ethisterone	100 mg
ethosuximide	100 mg
etocarlide	100 mg
flucytosine	100 mg
fluouracil	100 mg
fluphenazine decanoate dihydrochloride	100 mg
fluphenazine enantate dihydrochloride	100 mg
fluphenazine hydrochloride	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
ibuprofen	100 mg
imipramine hydrochloride	100 mg
indometacin	100 mg
isoniazid	100 mg
o-iodohippuric acid	100 mg
lanatoside C	100 mg
levodopa	100 mg
lidocaine	100 mg
lidocaine hydrochloride	100 mg
mefenamic acid	100 mg

Reference substance	*Package size*
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
metronidazole	100 mg
nafcillin sodium	200 mg
nicotinamide	100 mg
nicotinic acid	100 mg
norethisterone acetate	100 mg
ouabain	100 mg
oxacillin sodium	200 mg
papaverine hydrochloride	100 mg
pheneticillin potassium	200 mg
phenoxymethylpenicillin	200 mg
phenoxymethylpenicillin calcium	200 mg
phenoxymethylpenicillin potassium	200 mg
phenytoin	100 mg
prednisolone	100 mg
prednisolone acetate	100 mg
prednisone	100 mg
prednisone acetate	100 mg
procaine hydrochloride	100 mg
procarbazine hydrochloride	100 mg
progesterone	100 mg
propicillin potassium	200 mg
propylthiouracil	100 mg
pyridostigmine bromide	100 mg
riboflavin	250 mg
sulfamethoxazole	100 mg
sulfamethoxypyridazine	100 mg
sulfanilamide	100 mg
testosterone propionate	100 mg
tetracycline hydrochloride	200 mg
thioacetazone	100 mg
4,4′-thiodianiline	50 mg
tolbutamide	100 mg
tolnaftate	100 mg
trimethadione	200 mg
trimethoprim	100 mg
trimethylguanidine sulfate	100 mg
tubocurarine chloride	100 mg
vitamin A acetate (solution)	5 capsules[a]
warfarin	100 mg

[a] About 9 mg in 250 mg of oil per capsule.

Annex 3

TRAINING PROGRAMME IN DRUG ANALYSIS[1]

1. INTRODUCTION

The establishment of a new drug control laboratory in a developing country and the subsequent expansion of its activities is dependent on the local availability of properly trained staff. This applies both to the supervisory personnel (including the head of the laboratory) and to the analysts who will perform the tests (either single-handed or with the assistance of technicians).

Staff for drug control laboratories are usually recruited from schools of pharmacy but may also come from institutions specializing in various other branches of science. These graduates have adequate theoretical knowledge to perform standard analytical tasks but need a period of practical in-service training before they can be allowed to work independently.

In large established drug control laboratories, the practical training of newly recruited staff is usually accomplished by their temporary attachment to experienced analysts for periods of apprenticeship. In addition, a new staff member is sometimes required to attend briefing sessions on such matters as the internal organization of the laboratory, analytical documentation and reporting, and safety measures. However, such training is often impracticable in small laboratories and is out of the question when a completely new laboratory is to be established.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations, in its twenty-eighth and twenty-ninth reports, reviewed various aspects of the establishment and expansion of drug control laboratories in developing countries and came to the conclusion that the lack of adequately trained staff for governmental drug control laboratories is a major obstacle in the way of national programmes on improvement of drug quality (*1, 2*). The Committee is aware that some provision has already been made for individual training of drug analysts from developing countries (*2*). This arrangement, however, is more suited to the training of supervisory

[1] A group training course for recent science and pharmacy graduates in the practical and theoretical aspects of regulatory drug analysis.

staff or of analysts who already have substantial professional experience and are under consideration for promotion to supervisory positions. The Committee has therefore focused its attention on group training (*1, 2*) of recent graduates and has further developed the basic ideas presented in the twenty-ninth report of the Expert Committee (*2*).

The syllabus is designed to train people for the facilities provided in the model governmental drug control laboratories described in section 2 of this report. However, the training provided would enable the participants to adapt readily to the requirements of work in industrial control laboratories.

In oder to ensure that the training is of direct relevance to analysts from developing countries, it should be carried out in a well-equipped drug control laboratory in a developing country that has specialists in each discipline on its staff.

2. COURSE OBJECTIVES AND TYPES OF TRAINING

2.1 Course objectives

The main objective of the proposed training is to provide basic practical guidance on the analysis of pharmaceutical products. It is not intended to produce highly qualified specialists in the whole field of drug analysis. Special skills can only be acquired through long experience in laboratory work.

As a national drug control laboratory is not usually involved directly in the sampling of pharmaceutical products, sampling has not been included in the curriculum.

2.2 Types of training

Separate courses are proposed for chemical, microbiological, and biological methods of drug control.

The course dealing with chemical methods of analysis is comprehensive and reflects the present preponderance of chemical and instrumental methods among analytical procedures. It does not, however, include instruction on the use of complex instruments, such as nuclear magnetic resonance spectrometers, mass spectrometers, or autoanalysers, these not being provided for in the model laboratories described in section 2 of this report. Instruments,

such as polarographs, that are rarely used are discussed only from the theoretical standpoint.

The course on microbiological control emphasizes sterility testing, microbiological spoilage testing, potency tests for antibiotics and other specific drug substances, and the preparation and monitoring of culture media under local conditions. Methods used in the control of natural products are included, as well as the use of microscopic techniques for plant identification.

The biological control course is mainly concerned with pyrogen testing and specific safety tests. The testing of biological products such as vaccines and blood products is left out of consideration. Since many of the trainees admitted to the course will have received little formal training in pharmacology, sufficient theoretical knowledge must be provided to enable them to appreciate the objectives and importance of experimental work.

2.3 Educational background of trainees

The courses are intended for recent graduates in science or pharmacy with 3–4 years of education at university level. Among science graduates, preference should be given to those with detailed knowledge of analytical chemistry, biochemistry, or microbiology, but extensive practical experience is not required.

2.4 Training in more than one subject

Trainees desiring to be trained in more than one aspect of analysis should allow an interval of at least 1 year to elapse between courses, in order to ensure that each period of training is complemented by an extended period of practical experience.

3. DURATION OF TRAINING COURSES

3.1 General

It is envisaged that the courses in chemical control methods and in microbiological control should each last 6 months.

Since training in biological control is more restricted in its scope the syllabus can be completed in 3–4 months.

3.2 Teaching arrangements

The first week of each course provides an introduction to the general principles of quality control and analysis as they relate to procurement and distribution systems for pharmaceutical products.

It also develops a general awareness of all important aspects of quality control and a clear perception of the duties and responsibilities of an analyst. In particular it underscores the importance of instituting good laboratory practices in the interests of both efficiency and safety.

The practical training that follows also provides for discussions on the theoretical aspects of the use of instruments and the applicability and utility of individual methods, which it is recommended should occupy some 10–15% of the time available.

No guidance is given on the sequence of topics or the amount of time to be allocated to each. Detailed schedules can only be prepared locally on the basis of the facilities available.

In each course, the trainee, in addition to becoming familiar with the use of instruments and test methods, is expected to perform independently the full range of tests that he or she will subsequently meet in routine practice. Participants in the chemical drug control course should complete analyses of at least 25 pharmaceutical products, including both dosage forms and drug substances and in accordance with both pharmacopoeial monographs and manufacturer's specifications.

3.3 Course certificate

Trainees who successfully complete the whole course should be awarded a certificate indicating the nature of the course and its duration.

4. COURSE PROGRAMMES

4.1 Introductory subjects

- Intoduction to a national drug regulatory system and the activities involved in pharmaceutical inspection.
- The reasons for drug quality testing, including in-process quality control (good manufacturing practice requirements) and the analysis of finished products.

- An introduction to the statutory instruments in force locally (e.g., a drug and cosmetics act).
- The role of governmental drug control laboratories in relation to drug surveillance programmes.
- An introduction to the use of regional/national and international pharmacopoeias; selection of requirements and test methods suitable for the product.
- Operation of an analytical laboratory.
- Duties and responsibilities of an analyst.
- Good laboratory practices in governmental drug control laboratories.
- Maintenance of analytical instruments.
- Safety procedures in analytical laboratories.
- Record-keeping; the importance of properly documented laboratory work; maintenance of laboratory notebooks and the preparation of certificates of analysis.
- Reference standards and working standards; their importance and maintenance.
- Storage and care of samples.

4.2 Chemical drug control training programme

	Theoretical subject	Laboratory work
General		
• Checking and calibration of simple laboratory instruments, including analytical balances	+	+
• General quality standards and limit tests (sulfated ash, loss on drying, iron, arsenic, chloride, sulfate, lead, and heavy metals)	+	+
• Testing of packaging material	+	
• Preparation of reagents for the quantitative analysis of pharmaceutical products	+	+
• Evaluation of test results and the concept of statistical evaluation of analytical results	+	
Physical tests		
• Melting point determination and the concept of mixed melting points	+	+
• Viscosity	+	+
• Refractive index	+	+

	Theoretical subject	Laboratory work
Physical tests (*continued*)		
• Specific optical rotation	+	+
• Relative density	+	+
• Osmolarity	+	+
• Azeotropic distillation	+	
Gravimetric methods (test-tube methods)		
• Assay by the gravimetric method	+	+
Potentiometric techniques		
• Determination of pH	+	+
• Ion-selective electrodes	+	+
Titrimetric and related methods (employing both visual and potentiometric endpoint determination)		
• Acid-base	+	+
• Oxidation-reduction	+	+
• Non-aqueous	+	+
• Complexometric	+	+
• Karl Fischer	+	
• Polarography	+	
• Iodine value	+	+
• Saponification and acid values	+	+
• Nitrogen assay by the Kjeldahl method	+	+
• Oxygen combustion method	+	+
Spectrophotometric techniques		
• UV/visible	+	+
• Infrared	+	+
• Flame photometry	+	+
• Atomic absorption	+	+
• Fluorescence (especially in the analysis of vitamins)	+	+
Chromatographic techniques		
• Thin-layer	+	+
• Paper	+	+
• Column	+	+
• Gas-liquid chromatography	+	+
• High performance liquid chromatography	+	+
• Electrophoresis	+	

	Theoretical subject	Laboratory work
Pharmacognostic testing		
• Organoleptic examinations	+	+
• Microscopic examination of crude drugs	+	+
• Microchemical and phytochemical evaluation (alkaloids, glycosides, saponins, etc.)	+	+
• Physical evaluation (ash value, fluorescence, moisture content of crude drugs, extractive value)	+	+
• Physicochemical and chemical assay of crude drugs and galenicals	+	+
Dosage-form testing		
• General test procedures	+	
• The concepts of bioavailability and bioequivalence	+	
• Disintegration	+	+
• Dissolution	+	+
• Uniformity of mass	+	+
• Content uniformity of single-dose pharmaceutical products	+	+
• Tablet hardness and friability	+	+
• Assay of preservatives in a parenteral preparation	+	+
• Verification of added colouring matter in tablets and oral liquid preparations	+	+
• Limit tests for particulate matter in large-volume parenterals	+	+
Stability studies		
• Studies of the shelf-life of single-ingredient and multi-ingredient formulations at room temperature and at elevated temperature (accelerated decomposition) under different humidity conditions	+	+
Control of products requiring enzymatic determination		
• Control of pharmaceutical products containing pepsin, trypsin, papain, diastase, and pancreatin	+	+

4.3 Microbiological control training programme

Theoretical basis

- Morphology and fine structure of bacteria, fungi, and viruses; classification and nomenclature of bacteria; cultivation of microorganisms: nutritional requirements; ingredients, types, and preparations of culture media; physical conditions required for microbial growth; pure cultures and their characteristics; methods of isolating pure cultures; methods of preserving microorganisms.
- Effects of physical agents: pasteurization; sterilization by dry heat, moist heat, radiation and ethylene oxide; filtration; sterility testing.
- Effects of chemical agents; characteristics and classification of disinfectants; their selection and evaluation.
- Antibiotics and other chemotherapeutic agents; history of chemotherapy; classification of antibiotics; general chemical properties; mode of action; antimicrobial spectrum; development of resistance.
- Introduction to general biometry including the fundamentals of probability and significance calculations.
- Assay of antibiotics.
- Microbiological control of preparations not normally required to be sterile.
- Documentation and evaluation of test results.

Laboratory work

- *General microbiology*
  - —Preparation and dispensing of solid and liquid culture media.
  - —Sterilization of glassware.
  - —Small-scale preparation of sterile liquids.
  - —Aseptic transfer of microbial cultures.
  - —Microbiological method of testing the efficiency of a laminar-flow hood.
  - —Count of microorganisms: plate method and most-probable-number method.
  - —Study of the morphology of microorganisms by different staining methods:

(i) Gram staining;
(ii) spore staining;
(iii) capsule staining.

—Microbial limit tests for pathogenic organisms (*Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli,* and *Salmonella*).
—Sterility test for injectables:

(i) containing no inhibitor;
(ii) containing inhibitors (membrane filter method).

—Isolation of microorganisms from locally available material; their maintenance; maintenance of reference microbial cultures.
—Microbiological spoilage testing.
—Testing the effectiveness of antimicrobial preservatives.

- *Microbiological assay*

—Assay of antibiotics by the agar diffusion method, using both small plates (Petri dishes) and large plates, by means of the following techniques (including statistical analysis):

(i) 2 + 2 and 3 + 3 design for both large and small plates;
(ii) 6 × 6 and 8 × 8 Latin-square design for large square plates.

—Turbidimetric assay of antibiotics, with due attention to the experimental design.
—Assay of vitamins by both turbidimetric and agar diffusion methods.
—Bioautographic technique.
—Determination of the effectiveness of disinfectants (Rideal-Walker coefficient).

4.4 Biological control training programme

Theoretical basis

- General introduction to pharmacology.
- Absorption, distribution, biotransformation, and excretion.

- Dosage forms; different routes of administration and their influence on the biological response.
- Pharmacological classification of drugs, with representative examples.
- Modes of action of drugs with examples: extracellular and intracellular effects, membrane effects, enzyme effects, action on specific receptors, interactions.
- Responses in isolated tissues and intact animals; graded responses (oxytocin on rat uterus, vasopressin on cat blood pressure).
- Nature, source, and effects of pyrogens.
- Determination of dose and solvent for the pyrogen test on rabbits.
- Introduction to general biometry, including the fundamentals of probability and significance calculations.
- Quantal responses: minimum lethal dose (toxicity of stibogluconate sodium), percentage of animals responding to different doses (insulin assay in mice).
- Recording and evaluation of test results.
- Ethical responsibilities in using animals and consideration of alternatives to animal testing.

Laboratory work

- Animal house
  —Selection, handling, and care of laboratory animals; safety considerations; demonstration and instruction.

- Pyrogens
  —Preparation of pyrogen-free glassware, water, and solutions.
  —Test for pyrogens in rabbits.
  —*In vitro Limulus* amoebocyte lysate (LAL) test for the presence of endotoxins.

- Test for local irritation
  —Subcutaneous and intramuscular irritation tests for drugs and implants.

- Test for abnormal toxicity
  —Test to be carried out in mice.

- Histamine-like substances
  —Test of histamine-like substances on cat blood pressure (demonstration only).

- Bioassay
  —Insulin potency in mice
  —Heparin
  —Oxytocin (demonstration only).

REFERENCES

1. WHO Technical Report Series, No. 681, 1982.
2. WHO Technical Report Series, No. 704, 1984.