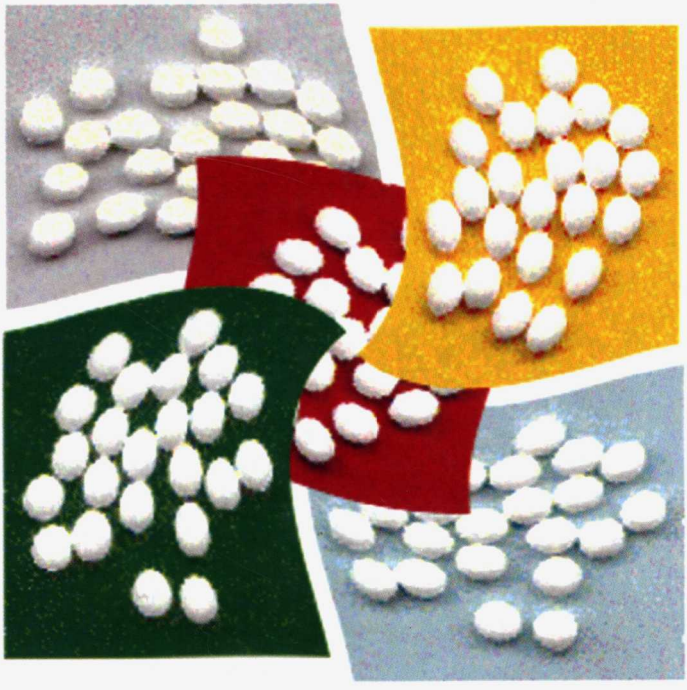
Quality assurance of pharmaceuticals

A compendium of guidelines and related materials

Volume 1



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The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences.

To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

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Introduction

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) ever since its inception. The setting of global standards is requested in Article 2 of the WHO Constitution which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products".

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

Without assurance that these drugs are relevant to priority health needs and that they meet acceptable standards of quality, safety and efficacy, any health service is evidently compromised. In developed countries considerable administrative and technical effort is directed to ensuring that patients receive effective drugs of good quality. It is crucial to the objective of health for all that a reliable system of drug control be brought within the reach of every country.

The supply of essential drugs of good quality was identified as one of the prerequisites for the delivery of health care at the International Conference on Primary Health Care in Alma-Ata in 1978. Similarly, the Conference of Experts on the Rational Use of Drugs, held in Nairobi in 1985, and WHO's Revised Drug Strategy, adopted by the World Health Assembly in May 1986, identified the effective functioning of national drug regulation and control systems as the only means to assure safety and quality of medicines. Yet the World Health Assembly continues to express great concern about the quality, safety and efficacy of medicines, particularly those products or active pharmaceutical substances imported into, or produced in, developing countries. In recent years counterfeit products have infiltrated certain markets in disquieting proportions. Since the founding of WHO, the World Health Assembly has adopted many resolutions requesting the Organization to develop international standards, recommendations and instruments to assure the quality of medicines, whether produced and traded nationally or internationally.

In response to these resolutions, the WHO Expert Committee on Specifications for Pharmaceutical Preparations, which was originally created to prepare *The international pharmacopoeia*, has made numerous recommendations relevant to quality assurance and control. Most of these recommendations, even if they

were made several years ago, are still valid. Thus far, however, most have been available only as separate sets of recommendations contained in annexes to various WHO Technical Reports. The recommendations are essential to all concerned with the quality assurance of medicines, but separate publication over a period of years made it difficult to recognize them as complementary parts of a comprehensive system of quality assurance.

To provide easy access to this information, the appropriate annexes are being reproduced in the two volumes of this publication. They are supplemented with other material relevant to the quality assurance of pharmaceuticals, some already issued in the form of WHO documents. The information is not necessarily presented in chronological order of original issue. Instead it is presented in logical sequence as a series of administrative instruments and technical elements of an overall quality assurance system. Readers should bear in mind that, in certain previously published texts, reference is made to WHO guidelines and other documents that have since been updated. Some of these updated texts are themselves included in the compendium and others are mentioned in this introductory section or listed inside the back cover of the book. All material relating specifically to good manufacturing practices (GMP) and inspection of pharmaceutical manufacturers will appear in Volume 2 of this publication. The actual standards for analytical controls are contained in *The international pharmacopoeia.* Other relevant publications include *Basic tests for pharmaceutical substances* and *Basic tests for pharmaceutical dosage forms.*

WHO has addressed not only pharmaceutical aspects of the quality of medicines, but also the intrinsic safety and efficacy of pharmacologically active substances. Advice on this has been published in the reports of the WHO Expert Committee on Essential Drugs, the *WHO model prescribing information* series, the *WHO pharmaceuticals newsletter*, and the quarterly *WHO drug information.* From there relevant information is carried over into the regularly updated United Nations *Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments.*

National drug regulation

The existence and functioning of a comprehensive drug regulatory system supported by legislation is a prerequisite for an overall quality assurance system. The first duty of a national regulatory authority is to register pharmaceutical products, thus defining the pharmaceutical market in the country. Only when this has been done will it be possible to distinguish between legally traded products and illegal and counterfeit ones.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations addressed this issue in its thirty-first report and adopted guiding principles for small national drug regulatory authorities. These guiding principles, later endorsed by the World Health Assembly in resolution WHA47.17, are reproduced in **Chapter 1**. The text gives advice on how to

organize national drug regulatory activities. The first section is devoted to general considerations such as the scope of drug control, basic responsibilities, licensing functions, product licences, manufacturers' and distributors' licences, new drug assessments, authorization of clinical trials, terms of reference of the regulatory authority, powers of enforcement, technical competence, advisory bodies and independence of operation.

The second and third sections of Chapter 1 address the administrative and technical aspects of the product registration or licensing process and give advice on the setting of priorities and on implementation by stages. It is anticipated that, once the initial drug registrations have been made, the registration process can be administered effectively if due advantage is taken of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and prudence is exercised when accepting new chemical entities. It is recommended that developing countries do not register a new chemical entity before it has been on the market for at least five years in a country with a sophisticated drug regulatory system that includes post-marketing surveillance, unless the chemical entity presents a real therapeutic advance in combating a major endemic disease. If this approach is respected, the major work of the registration process will be the pharmaceutical evaluation of products that have not been registered in the country of export or that have been produced locally.

In some countries with large public sector procurement of essential drugs, major challenges will be to coordinate drug registration and procurement, making sure that only duly registered products are purchased. This is the only way to take real advantage of favourably priced generic products. If the purchase of generic products is allowed regardless of their registration status, there is no guarantee of the products' quality with regard to stability and bioavailability, since pharmacopoeial specifications do not necessarily address these features.

A model software package for computer-assisted drug registration has been developed by WHO's Division of Drug Management and Policies in collaboration with the Health System Information Unit of the Pan American Health Organization, and has now been field-tested in several countries. It can be obtained from the Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland.

Product assessment and registration

The WHO Expert Committee on Specifications for Pharmaceutical Preparations has on several occasions discussed and adopted guidelines and other texts concerned with the assessment of pharmaceutical products and with registration requirements.

Herbal medicines

At its thirty-fourth meeting, the Expert Committee adopted guidelines for the assessment of herbal medicines. These guidelines, reproduced in **Chapter 2**, have been widely distributed to WHO Member States and were discussed at the Sixth International Conference of Drug Regulatory Authorities (ICDRA), held in Ottawa in October 1991. Their utility has been widely recognized.

Stability of pharmaceutical products

The problem of stability of pharmaceuticals has been addressed a number of times by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The introduction to this subject in the thirty-first report of the Expert Committee reads as follows:

> Inadequate storage and distribution of pharmaceutical products can lead to their physical deterioration and chemical decomposition, resulting in reduced activity and, occasionally, in the formation of toxic degradation products. Degradation is particularly likely to occur under tropical conditions of high ambient temperature and humidity; and it is not widely recognized that, because of the potential for chemical interaction between the active ingredients and excipients, drug dosage forms can be more vulnerable to degradation than pure drug substances.
>
> The stability of a specific product is thus dependent, in a large measure, on its formulation, and its expiry date should be determined on the basis of stability studies carried out by the manufacturer. Studies undertaken with a view to determining the stability of a product under temperate conditions, however, do not necessarily provide a reliable indication of its shelf-life in tropical climates. In such cases, additional proof of stability should be requested from the manufacturer, who should assume responsibility for formulating a product that is stable under the climatic conditions prevailing in the countries of destination. Relevant information should be specifically requested by the national regulatory authority in the importing country within the context of the WHO Certification Scheme . . . It is obviously impossible to obtain satisfactory assurances when a product is purchased through an intermediary if its provenance is unknown to the purchaser. For domestically produced products, the regulatory authority should evaluate stability data furnished by the manufacturer. The procurement agencies and the pharmacists responsible for drug distribution should ensure that they are supplied with adequate information concerning the proper storage and handling of each product.

Specific guidelines on the stability of drug dosage forms were annexed to the Expert Committee's report and are contained in Chapter 2. They provide a comprehensive statement on both the technical aspects of the subject and the

responsibilities that devolve upon the manufacturer and all agencies and individuals responsible for the product throughout the distribution chain up to the time of the drug's administration or delivery to the patient. The thirty-first report of the Expert Committee explains:

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

Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-fourth meeting, and are reproduced in Chapter 2. Recognizing that stability testing represents the evaluation of a pharmaceutical formulation in its final container, the Expert Committee emphasized that the same fundamental approach should be used for all products irrespective of whether the active ingredient was an established drug substance. Where sufficient information was already available on the chemical stability of the active ingredient, however, this could be taken into account. The availability of these guidelines was considered to be of special importance since they include advice on the stability testing of products for use in the more extreme climatic conditions found in many developing countries.

WHO has arranged for the conduct of accelerated stability studies on substances in the WHO Model List of Essential Drugs and has also sent out questionnaires to identify the products most likely to present stability problems. The accelerated stability studies are discussed in the twenty-eighth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. For newly introduced substances much information on stability is available, since in many countries this information is a mandatory requirement for registration of a new product and for determining expiry dates. By contrast, little information has been published on the degradation of long-established pharmaceutical substances (except for obviously unstable products) and, in many cases, their behaviour when exposed to extreme climatic conditions is uncertain.

For this reason, accelerated stability studies were carried out on long-

established essential drug substances under standardized conditions (e.g. 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-performance liquid chromatography and chemical determinations. The substances were additionally exposed to a temperature of 70 °C under the same humidity conditions for a further 3–5 days. Negative results provided conclusive proof of the stability of the substance even under highly adverse conditions. All tests were carried out with light excluded since it is easy to protect substances from light during storage.

A document entitled "Accelerated stability studies of widely used pharmaceutical substances under simulated tropical conditions" (WHO/PHARM/86.529) contains the results of these accelerated stability studies and is available on request from the Quality Assurance unit, Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland.

Interchangeability of multisource (generic) pharmaceutical products

The final text in Chapter 2 provides guidance on registration requirements to establish the interchangeability of multisource (generic) pharmaceutical products. In adopting these guidelines at its thirty-fourth meeting, the WHO Expert Committee on Specifications for Pharmaceutical Preparations was pleased to note that they had already been adapted for local use by a number of WHO Member States and that positive feedback had been received especially with regard to the flexibility and clarity of the guidance. The guidelines were designed to allow a step-by-step approach tailored to the stage of development of a particular registration system and the needs and priorities of the national health authorities. They were intended to assist drug regulatory authorities and international organizations involved in the procurement of pharmaceutical products, and to provide manufacturers with an indication of the data required. It was recognized that these guidelines were a first step: they would need to be supported by training and advice on implementation.

Good manufacturing practices and inspection

The guidelines approved by the WHO Expert Committee on Specifications for Pharmaceutical Preparations on good manufacturing practices (GMP) for pharmaceutical products will be reproduced in Volume 2 of this compendium, together with supplementary guidelines for biological products, the validation of manufacturing processes and the manufacture of investigational pharmaceutical products for clinical trials in humans and of herbal medicinal products. This publication will also contain guidelines on the inspection of pharmaceutical manufacturers and of drug distribution channels.

Distribution

The Twenty-eighth World Health Assembly, in resolution WHA28.66, enumerated a number of objectives relating to regulatory control of drugs. In consequence, in its twenty-seventh report, the WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the various elements of quality assurance in pharmaceutical supply systems (see **Chapter 3**).

Although parts of the elements described in Chapter 3 have been incorporated into or expanded in the guidelines for small national drug regulatory authorities, the text still provides a succinct review of quality assessment and assurance, premarketing quality assessment, and drug surveillance during marketing.

Pharmacists play an important role in the distribution of pharmaceuticals and must ensure that the service provided to patients is of appropriate quality. Guidelines on good pharmacy practice have been prepared by the International Pharmaceutical Federation in collaboration with WHO to encourage national pharmaceutical organizations to focus the attention of pharmacists in the community and hospital pharmacy sector on developing the elements of their services to meet changing circumstances. They provide a framework within which each country can set standards relevant to its own aspirations and needs.

The guidelines were presented in April 1997 to the WHO Expert Committee on Specifications for Pharmaceutical Preparations and will be included as an annex to the Committee's report. Copies of the text can be obtained from the Regulatory Support unit, Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland.

The international pharmacopoeia and related activities

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

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

Whereas earlier editions of *The international pharmacopoeia* had relied heavily on material taken from certain national pharmacopoeias, the third edition, of which four volumes have been published so far, aims to accommodate the needs of developing countries by offering sound quality standards for essential drugs on the basis (wherever possible) of classical procedures. Volume 1, published in 1979, describes general methods of analysis. Volumes 2 and 3, published in 1981

and 1988 respectively, contain quality specifications mainly for essential drug substances included in WHO's Model List of Essential Drugs. Volume 4 (1994) includes monographs on pharmaceutical substances, widely used excipients and dosage forms of essential drugs. Volume 5 (in preparation) will contain several new general requirements and additional test methods for substances and dosage forms, and a revised procedure for high-performance liquid chromatography. The volume will also contain specifications for the determination of more than 35 pharmaceutical substances and some 20 finished preparations in tablet form.

The role and objectives of *The international pharmacopoeia* are thus to a large extent to provide an alternative to some widely used national and regional pharmacopoeias that include sophisticated testing methods. Of course, if laboratory facilities permit use of advanced analytical methods, it is logical to analyse products according to the modern methods of such pharmacopoeias. Indeed, products may often be labelled as conforming to these pharmacopoeias. But where sophisticated testing is not possible, *The international pharmacopoeia* still allows verification of the quality of a product.

In its twenty-eighth report, the WHO Expert Committee on Specifications for Pharmaceutical Preparations summarized the functions and characteristics of *The international pharmacopoeia* and commented: "*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". At its thirty-fifth meeting, the Committee recommended that manufacturers in exporting countries be encouraged to use *The international pharmacopoeia* and to indicate such use in product information.

The international pharmacopoeia is developed in close collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, other specialists from government authorities, industry, the academic world and WHO Collaborating Centres. **Chapter 4** contains guidance for those preparing or commenting on monographs for inclusion in *The international pharmacopoeia.*

Analytical procedures used to control the quality of pharmaceutical substances and dosage forms must be adequately validated. Guidelines on validation, endorsed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, are included in Chapter 4. Since the extent to which validation is necessary is determined by the purpose of the analysis, judgement on the extent to which the guidelines need to be applied must be made on a case-by-case basis. These guidelines are directed primarily to the examination of chemical and physicochemical attributes, but many of the general principles are also applicable to microbiological and biological procedures.

Reference materials

Whenever necessary, monographs included in *The international pharmacopoeia* rely on the use of reference materials. These are provided either in the form

of International Chemical Reference Substances and Melting-point Reference Substances or as International Infrared Reference Spectra. Chapter 4 provides general guidelines for the establishment, maintenance and distribution of chemical reference substances. These include a section on the need for national and/or regional collections of secondary reference materials that have been calibrated against International Chemical Reference Substances. The chapter also contains recommendations for the preparation and use of infrared spectra in pharmaceutical analysis.

The guidelines on reference substances reproduced in Chapter 4 were published in 1982. These guidelines were revised in 1996 in the light of developments in analytical chemistry and international collaboration and to take into account established practice in the use of chemical reference substances for pharmacopoeial purposes. The revised guidelines are not intended to be specific to International Chemical Reference Substances, but are general guidelines for all bodies issuing chemical reference substances, and give advice on the establishment of both primary and secondary reference substances. The revised text was presented in April 1997 to the WHO Expert Committee on Specifications for Pharmaceutical Preparations and will be included as an annex to the Committee's report. Copies can be obtained from the Quality Assurance unit, Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland.

Some 180 International Chemical Reference Substances and some 60 International Infrared Reference Spectra have been produced and are listed in Chapter 4. Information is also provided on how to obtain them. The establishment of International Chemical Reference Substances and International Infrared Reference Spectra is continuing and new lists will be annexed to the report of the thirty-fifth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

A general list of reference substances for pharmacopoeial analysis is issued by the Quality Assurance unit, Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland, and is updated yearly. It provides current information on the availability and sources of reference substances. Most of these substances are prepared and issued by regional/national pharmacopoeial commissions or regional/national quality control laboratories on behalf of drug regulatory authorities. Each substance is generally established for a specific analytical purpose as defined by the issuing body. Use for any other purpose becomes the responsibility of the user and a suitable caution is included in the accompanying information sheet.

Basic tests

Simplified or basic tests for pharmaceutical substances have been published in *Basic tests for pharmaceutical substances* in 1986 and *Basic tests for pharmaceutical dosage forms* in 1991. In 1994, the WHO Expert Committee on Specifications for

Pharmaceutical Preparations suggested that the scope of the next publication on basic tests should be extended to include additional information on, and references to, other simple test methodologies. These are considered a valuable tool for primary screening and could play an important part in identifying counterfeit and spurious products. The third volume in the series of basic tests, which is in preparation for publication, will therefore refer to collections of simple tests other than those published by WHO. It will also contain details of basic tests for 23 additional pharmaceutical substances, 4 medicinal plant materials and 58 dosage forms. The substances covered by basic tests are mainly those included in WHO's Model List of Essential Drugs.

In its twenty-eighth report, the WHO Expert Committee on Specifications for Pharmaceutical Preparations stated: "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".

Basic tests do not need to be carried out by fully qualified pharmacists or chemists, but they should be performed by persons who have some understanding of analytical chemistry, such as required in courses for pharmaceutical assistants.

It is thus acknowledged that basic tests have a clearly defined but limited role. They have gained importance as screening tests to identify falsely labelled, spurious and counterfeit drugs.

Basic tests are developed in close collaboration with experts from all over the world and are tried in various laboratories to ensure their global applicability. Guidance on collaboration within the basic test programme, including a protocol for the development and verification of basic tests, was given in the twenty-ninth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations and is contained in **Chapter 5**.

Laboratory services

National laboratories for drug quality surveillance and control

An independent drug quality control laboratory is an indispensable element of a national drug quality assurance system, and is particularly important nowadays in the light of infiltration of distribution channels by counterfeit products. Laboratories are still missing in many developing countries. The reason for this is partly that, in the absence of any guidance on the basic requirements for such a laboratory, it was assumed for a long time that the costs would be so exorbitant that it would be beyond the resources of most developing countries.

In its twenty-ninth report, the WHO Expert Committee on Specifications for Pharmaceutical Preparations stated that every country, regardless of its stage of development, should consider investment in an independent national drug

quality control laboratory. The Expert Committee made recommendations directed to the many developing countries that have not yet created such a facility and do not have the resources to maintain a comprehensive system of control.

It should be recognized, in particular, that:

— simple procedures, such as tablet disintegration tests, are frequently of critical importance in eliminating seriously substandard preparations;
— a small laboratory directed by a competent, discerning individual will provide a persuasive deterrent to negligent or fraudulent manufacturing practices;
— the availability of complex automated equipment accelerates but does not necessarily raise the standard of analytical work. Moreover, such equipment performs reliably only when it is expertly maintained. Its operation may require the use of highly purified and expensive reagents.

Chapter 6 contains proposed models for a first-stage laboratory for drug surveillance, and a medium-size drug control laboratory. It provides advice on capabilities, premises, staff and equipment as well as on the scope of activities, factors influencing size and location of a laboratory, and the implementation of control laboratory projects. Even the smaller of the two model laboratories provides for the full pharmacopoeial analysis of more that 75% of WHO's Model List of Essential Drugs in accordance with the methods provided for in *The international pharmacopoeia.*

A document containing current prices for laboratory equipment is regularly updated and is available on request from the Quality Assurance unit, Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland.

Good practices for quality control laboratories

To complement its advice on setting up governmental drug control laboratories, the WHO Expert Committee on Specifications for Pharmaceutical Preparations included in its thirtieth report guidelines on good practices in governmental drug control laboratories. These, reproduced in Chapter 6, deal with management and operational issues affecting governmental drug control laboratories which analyse products for registration or during post-marketing surveillance. The scope of the guidelines ranges from 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 chemical and physicochemical analyses rather than with microbiological, pharmacological or other specialized test methods. The practices outlined are not fully applicable to quality control laboratories in manufacturing establishments, where test procedures and documentation may be different.

The guidelines are intended to be illustrative rather than prescriptive and need to be adapted to differing local circumstances such as the size of the laboratory. Alternative approaches to management are acceptable, provided that