REGULATION OF PHARMACEUTICALS IN DEVELOPING COUNTRIES

Legal Issues and Approaches

by

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INTRODUCTION

The four decades that have elapsed since the establishment of the World Health Organization have witnessed significant developments in the formulation and implementation of national drug policies. Legislation constitutes an important element in any such policy. The legal framework must take into account not only the policy objectives but also the administrative, social, and health infrastructures and the available manpower and physical resources. Inasmuch as there is no single drug policy model or structure that will suit every developing country, there is also no single legal model or structure that can be prescribed for all countries. Nevertheless, there are many aspects of legislation relating to pharmaceuticals that are of common concern.

This book provides an introduction to some of the legal issues relevant to the regulation of pharmaceuticals in developing countries and describes some of the possible approaches to the establishment of a regulatory framework. The book does not seek to be comprehensive in its treatment of the issues or in describing the various approaches. It deals mainly with the aspects that are of immediate concern to administrators in establishing modest control systems to facilitate the availability of safe and effective drugs of acceptable quality at reasonable prices.

In a text of this nature, covering different health care and legal systems, it is not always possible or feasible to make generalizations of universal validity. Certain comments and observations may not therefore be applicable to some countries because of differences in political, legal, and administrative structures or for reasons connected with social and economic factors. Furthermore, the health scenes in different countries represent a variety of policies, methodologies, and strategies tailor-made to cope with specific problems. It has been rightly pointed out in a recent WHO publication that “the health planning process, and the formulation of programmes to give effect to plans, have developed a mystique of their own”. This book seeks to demystify and simplify the formulation of legislation on pharmaceuticals and the operational and managerial process. Since it is addressed to health policy-makers and administrators, a deliberate attempt has been made to avoid, as much as possible, legal terminology. When it has been necessary to use such terminology, it has

been clearly defined and clarified in a manner comprehensible to those who do not have a medical or legal background.

Some of the chapters contain examples drawn from national laws and regulations. These references do not represent a comprehensive coverage of the legal situation in all developing countries, but are meant to be illustrative of the types of regulatory measure that have been devised. Most examples relate to laws and regulations that are currently in force. Whenever reference is made to a law that is no longer in force or has been allowed to lapse, the reason is that such a law illustrates a particular type of regulatory measure that may not have been replicated elsewhere or may not have gained wide currency. With few exceptions the legislative texts cited are to be found in the *International digest of health legislation*, published by WHO since 1948.
CHAPTER 1

The need for legislation on pharmaceuticals

There are several reasons — some obvious, some less so — why legislation dealing with pharmaceuticals is necessary. This chapter enumerates some of the reasons that have been advanced to justify legislative measures in this area.

Many legal systems are structured on the maxim or premise that “what is not prohibited by law is permissible”. A law serves the primary function of demarcating permissible from impermissible areas of activity. By sanctioning certain activities, subject to various rules and conditions, and by prohibiting other activities, a law clarifies what individuals (or corporate bodies) may and may not do. Laws dealing with pharmaceuticals can stipulate, for instance, who may import or manufacture drugs or who may prescribe certain categories of drugs. To take another example, certain drugs may be prohibited by law from being imported into the country, such importation thus becoming an impermissible (or illegal) activity.

To permit any policy to be implemented, there is a need to have various “authorities”. Such “authorities” may be individuals holding a particular office or having a particular title or designation (e.g., drugs controller) or an institutionalized agency or body (e.g., drugs control board). These authorities have to be entrusted with certain functions, duties, and responsibilities and they have to be vested with certain powers. These powers, duties, and responsibilities have to be laid down for the information and guidance of all concerned. If drugs can be imported only by a person who has a licence, there has to be an authority to call for applications for licences, to consider the applications, and finally to decide whether such licences will be granted or refused. If a licence is granted subject to certain terms and conditions, then appropriate action, by way of calling for an explanation or suspension of the licence or even its cancellation, will have to be taken in the event that any of the terms and conditions are infringed or violated. The power to grant a licence and to modify, suspend, or cancel it needs to be assigned to an authority. The exercise of certain powers affects the rights of individuals and there has to be a legal basis upon which the exercise of those powers rests. The powers, duties, and responsibilities that the implementation of a drug law
necessarily entails must be clearly defined in the legislation and any other instrument, such as a regulation or by-law, having the force of law.

Besides the authorities referred to above, a drug policy must of necessity deal with other individuals concerned with drugs, such as medical practitioners, importers, manufacturers, distributors, pharmacists, and consumers. These individuals play different roles in making drugs available and in ensuring that the needs of consumers are met. The law must demarcate their roles by specifying what they may and may not do. Pharmaceuticals constitute a special category of "consumer products". Their quality, safety, and efficacy are of paramount importance. For that reason, the law must specify who is entitled to handle them. For instance, a pharmacist must be professionally competent if he is to be entrusted with the responsibility of dispensing drugs. The degree of professional competence required will, of course, vary from country to country depending on the nature of the educational structure and local needs.

Legislation plays an important role in ensuring that the available pharmaceuticals are of acceptable quality, safety, and efficacy. Applicable standards and norms must be laid down in a legal instrument or other document having the force of law, and nonconformity with such standards and norms must entail appropriate penalties. Besides ensuring that the available pharmaceuticals are of acceptable quality, safety, and efficacy, legislation must also regulate their storage, availability, and distribution. A law may, for example, impose a condition that certain drugs must be sold or made available only to patients who have a prescription issued by a qualified doctor.

When seeking to introduce controls for hitherto unregulated activities, it is necessary to provide for situations in which there might be contraventions or infringements of the legal provisions. It is for this reason that the law must lay down the sanctions that will apply in the event of any nonconformity with legal provisions.

Having regard to the toxic effects of certain drugs and the consequent need to ensure that only drugs that are of acceptable quality, safety, and efficacy are made available to the right patients in the right circumstances, a strong case can be made for having a sound legal framework governing the manufacture and distribution of pharmaceuticals. Chapters 5 to 12 deal more specifically with the components or elements of this framework. The discussion in those chapters provides additional reasons why legislative intervention is warranted in this important area.
CHAPTER 2

General considerations applicable to legislation on pharmaceuticals

This chapter provides a short introduction to some of the constitutional, administrative, and legal principles and technical considerations that are applicable to health legislation in general and to drug legislation in particular.

Constitutional, Administrative, and Legal Considerations

The constitutional framework of a country determines to a great extent the permissible areas of regulation and the assignment and delegation of executive and administrative powers and responsibilities. Constitutional guarantees of rights and freedoms, such as the right to engage in trade and freedom of expression, have to be taken into account when regulatory measures interfering with such rights and freedoms (e.g., the restriction of imports of drugs and drug advertisements) are envisaged. Exceptions to guaranteed rights and freedoms are generally few. In most countries, considerations of public health and social policy provide sufficient justification for overriding or circumventing constitutional guarantees when framing specific and clearly articulated regulatory measures, provided these come within recognized permissible limits. Countries with a federal structure have to take cognizance of the need for jurisdictional and operational divisions of power and responsibility between the central or federal government and provincial governments.

Administrative considerations have a bearing on the type of institutional mechanisms and appellate procedures that are to be built into any legislation. The right to a hearing, before an application is rejected or refused or a licence is cancelled or suspended, for instance, is entrenched in many administrative law systems. In some countries, courts and tribunals exercise supervisory jurisdiction in respect of decisions, orders, and rulings of statutory functionaries and administrative and quasi-judicial bodies. Such supervisory jurisdiction can normally be excluded by legislation only on specific grounds. In any event, in most countries, courts of law have the jurisdiction to question the exercise of any statutory power for improper purposes or any decision made in bad faith.

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General principles of law determine the areas of permissible or lawful conduct and the rights of individuals to engage in various activities. Since what is not prohibited by law is generally considered to be permissible, prohibitions need to have some form of legal basis — common law, statutory, or judicial. In interpreting legal concepts, it is also necessary to take into account canons of statutory construction, which provide, for instance, that an expression will have the same meaning throughout the statute unless the context requires otherwise. Burden of proof is another area of concern. For example, if the legal system is structured on the presumption that a person is innocent until proved guilty, the burden is on the prosecution to prove guilt. Evidence has to be furnished in support of the charge. Expert evidence, such as that of a qualified drug analyst, might be required in certain cases to support the version of the prosecution and to contradict the position of the defence. However, by legislative provision the burden of proving certain matters or a state of affairs could be shifted, for instance, to the defence. For instance, the burden of proving that a drug conforms to certain prescribed manufacturing standards can be shifted to the defendant.

The concept of mens rea — criminal intent — is of particular relevance in relation to certain offences. If a statute uses concepts such as “wilfully” or “knowingly” in relation to an act or omission that is an offence, it would be necessary to prove the existence of such a frame of mind, in order to sustain liability; proof of mere commission of the act or responsibility for the omission will not suffice.

The principle of vicarious liability operates to transfer liability to someone other than the person who actually physically performed the impugned act or who was responsible for the omission. For instance, if an assistant in a pharmacy sells a drug without a prescription, in contravention of the law, the owner of the pharmacy might also be liable to prosecution if he had authorized the sale.

Terminology

A word of caution is necessary regarding terminology. In matters of legislation, a term or expression may have an entirely different connotation from the meaning attributed to it in common parlance. For this reason it is customary, and even desirable, to define various terms and expressions that are used in a statute. The nature of the definitions that are used will determine, to a great extent, the scope of the legislation. Clarity and precision are therefore particularly important in defining terms and expressions. Unless there has been a deliberate movement towards the harmonization of legislation, enactments of the same kind drawn up by different legal draftsmen in different countries may contain different terminology. Thus, the legal instrument on pharmaceuticals is likely to be known by different names in different countries. One country might call it a “drug law”, while another might call a similar piece of legislation a “drug
ordinance”, “decree”, “order”, or “act”. A variety of expressions are used even in respect of subsidiary legislation. The more commonly used are “regulation”, “subsidiary law”, “order”, “rule”, and “decree”. The authority empowered to make subsidiary legislation varies from country to country. In some countries the minister in charge of health is empowered to enact such legislation. Most legal systems require such legislation to be tabled in the legislature for approval and for publication in an official document available to the public. To identify the substantive basis of any rule of law in a particular country it is necessary to have an understanding of the nature of the law-making process and the precise terminology used in the country’s legal system.

In matters of doubt regarding the validity of the legislation or the interpretation to be placed on any provision or term or word in the legislation, it is desirable to consult a law officer, such as the attorney-general, or the legal draftsman. In a few countries, the ministry of health has a lawyer assigned to it, but not all countries have this facility. Health legislation, and in particular legislation on pharmaceuticals, has not received the attention of many lawyers in developing countries. There is therefore an urgent need to develop expertise in the area of drug legislation. Programmes of technical cooperation for the specialized training of lawyers and draftsmen need to be developed further.

**Harmonization of Policy Changes with Legal Changes**

Many developing countries have been slow to recognize that legislation constitutes an important input in the health sector and that the formulation of policies must be immediately followed by appropriate legislation to give effect to such policies. There is a need to take a close look at the legislation on pharmaceuticals when the national policy on drugs is formulated or modified.

**Time-frame for Changes in Legislation**

Changes in legislation are generally not intended to result in a dramatic turn of events. Gradual changes provide stability and time to marshal adequate resources to meet all situations and contingencies. It is best for far-reaching legal reforms to be introduced gradually to enable transitional arrangements to be made. Changes in areas such as importation and distribution networks and systems should be gradual, with a specific time-frame in which changes will become operational. The time lag between the announcement of the changes and the operational date enables alternative arrangements to be finalized. In relation to changes in imports, for instance, new sources of supplies have to be found, prices have to be negotiated, orders have to be placed, etc. Various issues of this nature need to be resolved and time is required to make all the necessary
arrangements. An example of a legislative change that was correlated with a time-schedule is the Decree-Law No. 51/79 of Cape Verde assigning to the State the exclusive right to import and manufacture pharmaceutical specialities and products. The Decree-Law, dated 9 June 1979, prescribed that private undertakings carrying out such activities must cease to do so by 31 December 1980. A more recent example of a similar exercise is the Bangladeshi Drug Control Ordinance No. 8 of 1982. It imposed various restrictions on the manufacture and distribution of drugs specified in schedules to the Ordinance. These restrictions were to become operative from a date specified in the Ordinance. By a subsequent amending Ordinance, No. 28 of 1982, the deadlines were extended.

In relation to phasing in legal changes, it should be noted that it is generally possible to provide for the different provisions or parts or sections of a law to come into operation from different dates. This allows adequate time to make preliminary arrangements to cope with additional responsibilities, functions, etc.
This chapter looks at the different approaches available for the provision of a legal framework on pharmaceuticals. Legal changes fall into two categories. The first category comprises substantive legal changes effected through a formal legal instrument, such as an act or ordinance or decree. The second category comprises subsidiary legal changes effected under the authority granted by a formal legal instrument. Regulations, by-laws, rules and orders are some examples of instruments that may embody subsidiary legal changes.

### Substantive Legal Changes

There are three possible approaches to effecting substantive legal changes:

1. **the revision or updating of existing legislation by way of amending legislation**;
2. **the replacement of existing legislation by an entirely new piece of legislation**; and
3. **the enactment of comprehensive legislation, where none existed previously, by the consolidation and revision of certain sections in different existing laws, supplemented by new or additional provisions**.

Each of the above approaches has particular advantages and features that merit further consideration. It is convenient to begin this discussion with approach (iii). If substantial changes have to be effected in a number of statutes, the process becomes cumbersome and time-consuming. Moreover, since the new provisions are embodied in several different statutory instruments, the process of identifying the new changes and the new legislative structures and linking up the different substantive and procedural provisions will prove tedious. If the various statutes to be amended come within the purview of different authorities or agencies, the new provisions may not be enforced uniformly unless there is an effective coordinating and monitoring mechanism. In a country that does not have a single piece of legislation dealing exclusively with pharmaceuticals, provisions applicable to pharmaceuticals may be found, for instance, in:
— the penal code (contamination or adulteration of drugs; misleading labelling and advertising, etc.);
— the import and export control act (licences for the import and export of drugs, etc.);
— the customs act (duty and tariffs on imported items and exemptions/restrictions on exports, etc.);
— the price control act (maximum wholesale and retail prices);
— the advertising act (prior screening of drug advertisements);
— the intellectual property code (trade marks and patents);
— the medical practitioners act and/or pharmacy act (prescription liability, licences for distribution, retail outlets, etc.); and
— the industrial promotion and regulation act (prior approval for the establishment of new industries).

In addition to the above, there are, of course, many other statutes, such as those dealing with dangerous drugs, narcotics, food, poisons, cosmetics, and medical devices, all or some of which would have overlapping provisions sufficiently wide to cover certain aspects of the regulation of pharmaceuticals. Even in a country where the number of statutes having provisions relating to drugs is relatively low, a consolidated enactment may be desirable for several reasons. Such an enactment facilitates understanding of the new legal framework. The seriousness with which the country is implementing a drug policy is reflected to some extent in its enactment of a comprehensive piece of legislation setting out, with precision and clarity, the legislative input in relation to the overall policy. Another advantage is that future policy changes that require amendments to the law can be easily accommodated within the framework of a single legislative instrument by appropriate modifications to the consolidated enactment without having to re-examine the entire code of relevant laws to identify which of the statutes need to be amended. Moreover, there is always the risk that amendments to isolated statutes, which are otherwise of marginal significance, may pass into oblivion before the impact of the changes is fully realized.

Approaches (i) and (ii) above are closely interlinked. It is often difficult to decide which of these two approaches is preferable in a particular situation. The nature and magnitude of the contemplated changes and the ease with which these changes can be accommodated within the existing legislative framework may provide clues as to which approach is preferable.

If the contemplated changes are not too complicated and can be conveniently built into the existing framework, revision or updating can be effected by way of amending legislation. In many countries, amendments to the existing legislation can often be finalized with little administrative and procedural formality, attention being focused primarily on the implications of the amendments envisaged rather than the entire legislative structure and the general working of the law. Judicial decisions on various conceptual and operational issues based on the statute would continue to have the same binding force or validity if the statute were kept
intact and only certain provisions amended. If the statute were repealed and replaced, the binding force of previous judicial decisions would be considerably diminished even if most provisions remained unchanged. In any event, there is a greater element of doubt as to the attitude of the judiciary when a new statute has to be interpreted, as compared with a situation where several judicial decisions have, over the years, followed the same line of reasoning in relation to particular provisions.

Far-reaching legal changes generally require an overhaul of the entire legislative scheme. Changes that are substantial, both in their number and in their implications, are best incorporated in an entirely new statute. In the absence of a new legislative text, it might be difficult to appreciate the full significance of the changes.

It is not possible to lay down rigid criteria to determine which method is preferable in a particular situation. In case of doubt, the law officer or the legal draftsman should be able to advise on the best course of action. National examples illustrating each of the three approaches are given in Annex 1.

**Subsidiary Legal Changes**

Legal systems generally differ as to the manner in which subsidiary changes have to be effected. Subsidiary changes are those that deal with matters of secondary importance, such as details and explanations, rather than with fundamental principles, but that are referable to a general rule, principle, or power set out in the main legislative text. For instance, the main legislative instrument might empower the issue of licences to enable drugs to be imported but the format of such licences and the general conditions subject to which such licences may be issued might not be set out in the main text itself. Matters of this kind are normally dealt with in instruments that are in the nature of regulations, orders, by-laws, rules, etc. The generic expression “delegated legislation” or “subsidiary legislation” generally encompasses instruments of this nature. However, there is no uniformity in the terminology used by different countries.

The authority empowered to enact regulations, orders, and similar instruments varies from country to country. As regards pharmaceutical legislation, the appropriate authority may be the minister in charge of health, the head of the health services, the regulatory agency, or the control board. The holder of an office or an authority has to be specially empowered to enact these instruments. Normally the power to make instruments also includes the power to repeal and replace them. However, the power to make instruments of the kind discussed is not unlimited. In many legal systems, the parliament or similar supreme law-making body has the power to review and approve such instruments. The requirement that these instruments must be published, usually in a government publication, and that they should be tabled in the legislature enables control to be exercised over the manner in which they are prepared and over their scope and content. The instrument must deal with matters that are within the
general power of the regulation-making body and must be geared to give effect to the general principle or rule enunciated in the main legislative text. A regulation that is outside the scope of the regulation-making power is invalid and has no force or effect in law.

There are certain advantages to be gained from conferring a wide and extensive power to make subsidiary or delegated legislation. In fact, it is often necessary to confer such a power; technical matters, for instance, are best left to be decided after consultation with the appropriate agencies and personnel, and these matters can be formulated and set out in the instrument in the manner best suited for the purpose. On the basis of feedback and experience, the details and procedures set out in the instrument can be revised from time to time. This revision process is much simpler than the substantive law-making and revision process, in that the instrument can easily be amended (or, alternatively, revoked and replaced) and thereafter tabled in the legislature or other appropriate forum for approval. Experience from most parts of the world suggests that approval of subsidiary or delegated legislation is often nothing more than a procedural formality. Furthermore, certain legal systems do not require all instruments and their revisions to be tabled in the legislature or other appropriate forum. For instance, the power to add or delete various substances from a schedule can usually be exercised by making an order that requires hardly any follow-up formalities, except perhaps the publication of the order.
CHAPTER 4

The evolution of a law dealing with pharmaceuticals

This chapter considers the procedural steps in the formulation and finalization of a law on pharmaceuticals.

Within the context of the national drug policy and the other policy measures, strategies, and programmes of action envisaged by the government, it is first necessary to identify the matters to be covered by the legislation. The objectives of the legislation must be clearly defined in relation to the available resources and existing infrastructure, as well as to future needs. For instance, if one of the objectives is that only registered drugs should be on the market, decisions must be taken from the outset on a framework for the mechanism of registration, the procedure to be followed in applying for registration, and the documentation to be submitted. It is with such considerations in mind that the legal principles and rules must be formulated.

Before a law can be drafted, there must be consultations with appropriate personnel, consideration of policy documents, collection of information regarding the state of the art in other countries, and consideration of likely changes and reforms in the health sector. The nature of the consultations required will depend on the extent to which information is readily available and the type of consensus that will be helpful in identifying real needs and possible approaches and solutions. It is necessary to have prior consultations with the professional and other groups concerned, such as medical practitioners and pharmacists, and with representatives of industry. Inasmuch as the successful operation of a drug policy depends on the collaborative effort of all concerned, prior consultations might allow conflicting ideologies to be reconciled and misconceptions to be clarified; at the same time, they should help to develop a greater sense of commitment to work in harmony to achieve the overall objectives.

Once the basic information has become available, how does one set about drafting the law?

The starting-point of any drafting exercise is the preparation of an inventory of laws and regulations already existing on the statute book. Such an inventory enables a proper assessment to be made of the adequacy or otherwise of the existing legal framework in meeting the new objectives and the type of legislative instruments required for the new purposes. An assessment of this nature will highlight the gaps to be filled. Depending on
the nature of the matters to be covered in the legislation, recourse can then be had to one of the approaches to law-making described in Chapter 3.

The ultimate responsibility for the preparation of the law is with the legal draftsman, but there must be constant interaction between the officials concerned and the draftsman. The purpose of this interaction is to permit an exchange of views on the legal, technical, and practical problems in incorporating essentially health-related concepts into a legal document and translating essentially legal concepts and formulae into action. Consideration of the draft legislation at a meeting attended by all the responsible authorities, relevant agencies, representatives of the pharmaceutical industry, and relevant interest groups, together with the legal draftsman, has been found by many countries to be most useful. Exposure of the draft to a group of people with wide and varied interests and responsibilities enables appropriate refinements and modifications to be made before the legislation is finalized for approval by the government.

The passage of a bill through parliament involves various stages. It is outside the scope of this chapter to discuss these procedural matters. However, one observation that may be made here is that the minister or other functionary who will be introducing the bill in the parliament and who has to explain its objectives, scope, and content must have a complete and detailed brief for his guidance. It is often useful to include in the brief a comparative study of what has been done in other parts of the world with similar problems or similar policies.

The preparation of a schedule regarding the various steps to be followed and the work to be done not only helps to lubricate the wheels of the administrative and executive machinery, but also facilitates the synchronization of other related activities in the implementation of the drug policy with the different phases of the law-making process.
CHAPTER 5

Legislative models and structures for the regulation of pharmaceuticals

This chapter provides an overview of the different legislative models and structures that have been devised in relation to the regulation of pharmaceuticals in developing countries.

The present state of the art provides profiles of three different legislative models and structures, which may be described as: (a) basic elements model I; (b) basic elements model II; and (c) the advanced model.

These will now be considered in detail.

Basic Elements Model I

The concept of "basic elements of drug legislation" owes its genesis to an exercise undertaken by WHO. At a Consultation held in Geneva in 1981 by the Action Programme on Essential Drugs, an attempt was made to identify the basic elements that must be contained in the drug legislation of any developing country, whatever its stage of development.¹ These basic elements, therefore, represent the minimum framework that a country must have. However, the stage of social and economic development and the nature of the health care infrastructure might warrant a legislative instrument with more elaborate provisions.

The basic elements identified at the Consultation are listed below with some slight modifications.

A. General provisions

(1) Title: in addition to a long title reflecting the scope of the Act, a short title, if necessary.

(2) Purposes: the purposes of the Act are (a) to ensure that, in the overall national pharmaceutical supply system, safe, effective and inexpensive drugs of good quality reach the consumer, (b) to discourage the abuse of drugs, and (c) to ensure fair trading practices in the pharmaceutical sector.

¹ Report of a consultation on basic elements of drug legislation and regulatory control for developing countries. Unpublished WHO document, DAF/81.3.
(3) **Extent:** the territorial area to which the Act applies, defined in accordance with constitutional and administrative requirements and local conditions.

(4) **Application of other laws:** a statement that the Act is in addition to other laws, e.g., on narcotics, poisons, pharmacy, currently in force. However, in the event of any conflict the provisions of this Act would prevail.

(5) **Definitions:** definitions of various terms and concepts used in the Act for purposes of interpretation.

**B. Specific provisions**

(1) **Control of import of drugs**
- conditions for importation
- persons qualified to import
- type(s) of licence or certificate required for importation
- fees
- manner of storage of drugs at places of import, pending release
- record-keeping procedures with respect to imported drugs

(2) **Control of export of drugs**
- conditions for export
- persons qualified to export
- certificates to be issued for export
- fees
- record-keeping procedures

(3) **Control of manufacture**
- premises and equipment
- technical personnel
- quality assurance system
- type of licence required for manufacture
- hygienic standards
- shelf-life
- in-process inspection
- record-keeping procedures
- fees for licences

(4) **Control of distribution, supply, storage, and sale**
- manufacturers
- importers
— wholesalers 
— retail pharmacies and other authorized channels of distribution 
— governmental and private institutions and suppliers

C. Other provisions

Authority for the regulation of:

(1) Labelling
— of the container
— of the outer package
— inclusion of package insert

(2) Information and advertising
— prohibited advertising (for certain diseases, drugs, etc.)
— conditions for promotional activities to the general public and professionals

(3) Drug registration
— notification, authorization, registration of pharmaceutical products
— withdrawal
— renewal of registration
— clinical trials

(4) Scheduling
— sales categories of drugs (provided for in different schedules)
— conditions for sale of drugs (prescription and non-prescription drugs, etc.)

(5) Imposition of fees

(6) Price control

D. Drug control administration

(1) Organization and function
— central agency, or department, with an appropriate and effective structure to discharge its responsibilities for drug registration and control of manufacture, import, export, distribution, labelling, pricing, information, and advertising
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- drug registration board or committee for registration, re-registration, evaluation, cancellation of registration, etc.
- inspectorate services responsible for inspection of enterprises, sampling from ports, warehouses, wholesale and retail establishments, and manufacturing enterprises
- laboratory services and institutions for quality control
- advisory bodies and expert technical committees

(2) Appeals against decisions of the drug control agency or department
- possibility of reconsideration
- possibility of appeal to an appellate board

E. Prohibitions, offences, penalties and legal procedures

(1) Prohibition of specified activities
(2) Penalties for each offence based on magnitude and occurrence
(3) Legal procedures for offences

F. Powers to make rules and regulations

The Act should designate and empower the appropriate authority to establish schedules, rules, and regulations for the purpose of the Act, in respect of all or any of the matters with which it is concerned.

G. Repeals and transitional provisions

(1) Repeal of sections of existing laws in conflict with the Act
(2) Transitional period between the time of promulgation of the Act and its commencement.

H. Exemptions from the provisions of the law

Exemptions in relation to substances, personnel, etc.

The above elements will be discussed at length in subsequent chapters. For the present, it may be noted that there is a set of elements which, with slight modifications and adaptations, can meet the initial requirements of any country planning to launch a drug policy. These elements, though termed "basic", are sufficiently wide and varied in their scope to meet most of the objectives of any modest national drug policy. Conversely, many developing countries will be able to implement a national policy even without all these basic elements. For instance, provisions covering drug manufacture would not be of much practical relevance to a country that has no immediate plans to engage in the domestic production of drugs.
An Intercountry Consultative Meeting on Drug Legislation for countries of the South-East Asia Region organized by WHO was held in Kathmandu in April 1983. At this Meeting it was underlined that the basic elements identified at the Geneva Consultation (see p.19) could be developed further to facilitate the implementation of the national drug policy of certain countries. It was suggested that the following elements might be added to the list of elements in model I.

A. Control of distribution, supply, storage, and sale

(1) Sales promotion personnel  
(2) Monitoring of adverse drug reactions

B. Subsidiary items

(1) Ethical standards  
(2) Voluntary codes of practice  
(3) Drug abuse: preventive education programmes for consumers  
(4) Compulsory patent licences in respect of patents that have not been used or exploited for a reasonable period of time  
(5) Compensation for drug victims

The elements identified as possible additions are of relevance to developing countries in general and not only to the group of countries in the WHO South-East Asia Region.

Advanced Model

A more detailed analysis of the elements identified at the two consultations referred to above and an examination of national laws indicate that there are still several other elements that can be added. For instance, there is no reference in either of the two models to the use of generic names instead of brand names. The use of generic names in importing, prescribing, and dispensing drugs might have substantial financial advantages. Another area that deserves attention is the system of patents and trade marks. For several years, attempts have been made to develop strategies aimed at striking a balance between the needs of inventors and manufacturers for protection and the needs of countries to have access to drugs that are inexpensive and that, if the need arises, can be manufactured locally. This problem will be discussed further in a subsequent chapter. Other
areas that are not reflected in the elements listed above but that are of immediate concern are: (a) the preparation of a national formulary and pharmacopoeia; (b) the establishment of a drugs fund for innovative drug activities, with provision for tax-free donations, to cover expenses; (c) the provision of a package of monetary and tax incentives to promote the domestic production of drugs (at least those that are essential); (d) the promotion of drug research and innovation by providing tax and other incentives; (e) the recall of banned drugs; and (f) the dissemination of information on such questions as the toxic effects of drugs.

A drug law that contains all these elements would be representative of what might be called the "advanced model".

Choosing and Implementing the Appropriate Model

The distinctions between the different models described above reflect the efforts to evolve appropriate legal structures for developing countries. A country enacting a drug law may select elements from any one of these models. Similarly other elements that countries consider appropriate can be accommodated within any one of the models. The guiding principle in selecting elements is that the country has or is likely to have the administrative capability and the resources to enforce the legal provisions. A law with modest aims and objectives that is properly implemented is preferable to an elaborate legal structure that is destined to remain good law only on paper. An unenforced law or regulation "becomes a museum piece from the outset".¹

Whatever model is chosen, a drug law depends on several inputs and resources for its implementation. There has to be a strong political will and commitment. In designing the legal structure, cognizance needs to be taken of the availability of inputs and resources and the implications involved in employing them for this particular purpose. Table 1 sets out some of the inputs, resources, and commitments that are required to make a drug law operational. These are listed in relation to specific functions and purposes. It must be stressed, however, that this table is not intended to be exhaustive, but rather to highlight the nature of the "official" or "governmental" commitments required and the inputs and resources necessary to ensure that the legal machinery operates smoothly and that progress is made. The implementation of a drug law requires funds for the purchase of drugs and depends on medical practitioners, pharmacists, sales outlets, etc., but, in the interests of simplicity, these aspects have been omitted from the table. Nor does the table include sources of funding, such as registration and licensing fees, or the utilization of existing resources and personnel.

Table 1. Inputs, resources, and commitments needed to make a drug law operational

<table>
<thead>
<tr>
<th>Input/resource/commitment</th>
<th>Specific function/purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel requirements</td>
<td>Regulatory activities</td>
</tr>
<tr>
<td></td>
<td>(licensing, registration, etc.)</td>
</tr>
<tr>
<td></td>
<td>Monitoring, inspection and surveillance</td>
</tr>
<tr>
<td></td>
<td>Enforcement</td>
</tr>
<tr>
<td>Physical requirements/infrastructure</td>
<td>Office space for regulatory and enforcement personnel</td>
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<tr>
<td></td>
<td>Equipment</td>
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<tr>
<td></td>
<td>Quality control laboratories</td>
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<tr>
<td></td>
<td>Vehicles for distribution, inspection, and enforcement activities</td>
</tr>
<tr>
<td>Technical requirements</td>
<td>Pre-service and in-service training</td>
</tr>
<tr>
<td></td>
<td>Establishment of drug manufacturing</td>
</tr>
<tr>
<td></td>
<td>processes, packaging, etc.</td>
</tr>
<tr>
<td></td>
<td>Collation of data</td>
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<tr>
<td></td>
<td>Dissemination of information</td>
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<tr>
<td>Financial requirements</td>
<td>Capital and recurrent expenditure</td>
</tr>
<tr>
<td></td>
<td>Technical programmes</td>
</tr>
<tr>
<td></td>
<td>Payments for patents, royalties, etc.</td>
</tr>
<tr>
<td></td>
<td>Payments for consultants, etc.</td>
</tr>
<tr>
<td></td>
<td>Publications (forms, licences, pharmacopoeia, etc.)</td>
</tr>
</tbody>
</table>

While the inputs, resources, and commitments listed in Table 1 are required in any event, the identification of the precise mix of elements to be incorporated in the law depends on a number of factors, such as:

(a) the level of the country's social, economic, and political development;
(b) the nature of the health infrastructure;
(c) trade and industrial policies and programmes; and
(d) possibilities of cooperation with and support from other relevant national, regional, and international agencies; public and private sector establishments; professional groups; drug manufacturers and importers; etc.
The scope of legislation on pharmaceuticals

The scope of a law on pharmaceuticals depends on the range of elements (see Chapter 5) to be included in the law.

This chapter deals with two issues that are relevant to the problem of determining what exactly should be the scope of a law on pharmaceuticals: (a) the coverage to be accorded to substances and items other than drugs; and (b) the nature of the conceptual problems encountered in incorporating various elements or components into a legal instrument.

Coverage of Substances and Items other than Drugs

Drug legislation in developing countries can be divided into two broad categories, namely:

(a) laws dealing only with drugs (i.e., pharmaceuticals); and
(b) laws that cover other substances and items as well as drugs.

Substances and items other than drugs covered in the same legislation, include: food; cosmetics; poisons; medical devices; narcotics; psychotropic substances; chemicals; pesticides, insecticides and herbicides; blood, blood products and vaccines; drugs or preparations used in traditional systems of medicine (e.g., Ayurveda, homoeopathy); veterinary products; and toiletries and detergents.

Neither the historical evolution nor present trends provide evidence that the direction in which drug legislation has moved or is moving shows any clear or consistent pattern. For instance, Sri Lanka, which had a Food and Drugs Act from 1949 (Act. No. 25), replaced it in 1980 with a law dealing with drugs, cosmetics and devices (Act No. 27). In the same year, two new statutes dealing with food (Act No. 26) and pesticides (Act.No. 33) were also enacted. India began with a Drugs Act in 1940 (Act No. 23) and gradually extended its scope to cover cosmetics (Act No. 21, 1962), traditional medicine (Act No. 13, 1964) and, finally, after more than four decades, medical devices (Act No. 68, 1982). Pakistan enacted new legislation in 1976 dealing only with drugs (Act No. 31). In Bermuda, a new law
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was enacted in 1979 (Act No. 26) dealing with both drugs and poisons. Sometimes a single statutory instrument, such as a Public Health Code, may even cover five or six substances.

It is not easy to decide whether other substances or items should be covered along with pharmaceuticals and, if so, what those items should be. There are no rigid rules or criteria to determine whether there should be a separate law on pharmaceuticals. Though it would seem that a separate law might facilitate enforcement, the policy to be adopted is a matter to be decided entirely by national authorities. Some of the issues to be considered in deciding whether a separate statute on pharmaceuticals is warranted or not are listed below. This list is by no means comprehensive, but the topics included are indicative of the range of questions to which national authorities must address themselves.

1. **The nature of the existing legal framework**

   If there is existing legislation covering different substances, how has the system worked over the years? What are the legal, administrative, and operational problems encountered as a result of a multiplicity of substances being covered by the same statute? What are the advantages that have accrued to the regulatory authorities and administrators as a result of the combination of several substances in the same statute? As a matter of priority, is it necessary to cover any other substances in addition to pharmaceuticals?

2. **Common factors**

   What are the elements or components in the proposed legislation on pharmaceuticals that are common to other substances and items? Is a common regulatory agency feasible? Are the control mechanisms and enforcement strategies identical? Are the identical or overlapping provisions so numerous that two or more different enactments would be superfluous or redundant?

3. **Characteristic or material differences**

   Which of the special provisions contemplated in respect of pharmaceuticals would be inapplicable to other substances and items? Will the legislative scheme become distorted or complicated if such special provisions are incorporated in a separate chapter or part of the same legislation? Are the provisions that are not common or similar readily distinguishable?

4. **Advantages and disadvantages of combined legislation**

   If control and enforcement efforts have to be spread over more items and if time and resources have to be divided, will it impede the proper implementation of the provisions relating to pharmaceuticals? Can available resources be better utilized and economies of scale achieved by allo-
cating more responsibilities and duties to the same institutions and personnel? What are the manpower and physical resources that could be kept intact if several substances came under the purview of a single authority? What is the capability of administrators and enforcement personnel to shoulder greater responsibility but at the same time effectively discharge their duties in relation to a number of different substances?

Whatever the final decision on the inclusion of other items or substances along with pharmaceuticals, it needs to be emphasized that the terms and expressions used in the statute must be clearly defined and the applicable provisions clearly demarcated. Countries with a single legislative text dealing with other substances, in addition to pharmaceuticals, have adopted different methods to identify the applicability of the relevant provisions. In the Indian legislation (Act No. 23, 1940), different chapters deal with drugs, traditional medicines, etc. On the other hand, in Bangladesh (Ordinance No. VIII, 1982), the expression “drugs”, wherever used, is intended to cover also substances used in traditional systems of medicine, while the expression “medicine” covers only pharmaceuticals. The use of expressions such as “article” or “substance” enables the scope of the legislation to be gradually extended, should there be a need for such extension. Authorities must, however, ensure that there is no room for any doubt as to whether certain provisions were intended to apply only in respect of pharmaceuticals or not.

Conceptual Issues

The extent of the applicability of a law on pharmaceuticals depends, to a great extent, on the scope of the concepts incorporated in it. A limited definition of the expression “drugs”, for instance, might result in many pharmaceutical substances falling outside the purview of regulatory controls. For this reason, it is necessary to identify clearly what types of drug need to be covered by the legislation. In the present book, for instance, the expressions “drugs”, “substances”, “pharmaceuticals”, and “medicaments” are used as synonyms unless the context has made it clear otherwise. However, in national legislation, these expressions might have different connotations. By and large, the expression “drugs” has been favoured by most countries. However, there are exceptions. Some laws use both “drugs” and “medicines” in addition to other expressions. Under the 1982 Bangladeshi Drugs Control Ordinance No. VIII, section 3, the expression “drugs” is defined as “...any substance exclusively used or prepared for use in accordance with the ayurvedic, unani and homeopathic or biochemic system of medicine” and thus includes drugs used in traditional systems of medicine. In Fiji, the Pharmacy and Poisons Ordinance No. 5 contained the expression “drugs” from 1958. The amending legislation of 1980\(^1\) has other definitions such as “medicine”, “medicinal purpose”, and “herbal remedy”. In some laws, for instance the

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\(^1\) Pharmacy and Poisons (Amendment) Act No. 2 of 1980.
Pharmaceuticals and Poisons Act of the United Republic of Tanzania, No. 9 of 1978, the expression “drugs” has been defined to include any “medicine”, “medicinal preparation” and “therapeutic substance”. Besides this definition of “drugs”, the Act also contains definitions of “medicine”, “pharmaceutical product”, “poison”, and “substances recommended as medicine”. The 1979 Drugs Act of Thailand (Act No. 3) contains separate definitions of the following expressions: drugs, modern drugs, old-fashioned drugs, dangerous drugs, specially controlled drugs, external drugs, specific place drugs, common household drugs, packaged drugs, and herbal drugs.

The use of several expressions might lead to confusion unless the concepts are clearly defined. Clarity facilitates compliance with the law and its enforcement.

In relation to any category of pharmaceuticals, such as those listed above, it is possible to have subcategories or specifications. For instance, there can be different regulatory provisions in respect of pharmaceuticals available only on prescription and those that are freely available. To take another example, the law can provide for sanctions in respect of misbranded drugs, spurious drugs, adulterated drugs, and counterfeit drugs.

The formulation of a definition or description is an activity that has to be undertaken after deciding on the type of general requirements and special requirements to be incorporated in the statute. If the special requirements necessitate some kind of identification, an appropriate definition or description should be formulated.

Some legislative instruments are divided into a number of different parts, chapters, or sections, with general definitions in one part, chapter, or section. Such a structure permits special requirements with common elements to be incorporated in a particular part, chapter, or section in the legislative instrument, with a separate definition or description applicable only to the provisions contained in that particular part, chapter, or section. Another possibility is to preface the general definitions with words of limitation indicating that the definitions apply in respect of all the relevant provisions unless a contrary intention is expressed or the context makes it clear that a different interpretation is to apply. Such a formula enables a provision to be drafted in any particular way together with a definition or description applicable only for the purposes of that provision.

Definitions and descriptions of terms and concepts in a law on pharmaceuticals fall into two broad categories. The first category comprises medical or scientific terms and concepts. These need to be formulated by those who are familiar with established medical or scientific usage. For instance, the definition of “bioavailability” or “active ingredient” is not one that a layman or a legal expert could formulate on his own. Concepts and terms that have a specific connotation in medicine or science should be incorporated in a law in such a manner as to reflect their established meaning or intent, though in translating such concepts or terms into legislative language appropriate modifications may be made to suit not only local circumstances but also the legislative purpose. For instance,
clinical trials of a particular product may entail a certain number of phases in order to conform to generally accepted scientific standards, but a country might be prepared to grant exemptions in respect of certain phases and rely on data from trials in other countries. In such a situation, the concept of "clinical trials" in the legislation must reflect only what is deemed necessary to satisfy local requirements. Expressions that are of a medical or scientific nature must receive the approval of those who are familiar with them. The legal draftsman must be furnished with specific examples of generally accepted definitions or terminology with an indication as to whether any modifications are required.

The second category of definitions comprises terms and concepts of a legal or general nature. Terms such as "possession" and "sale" may have specific jurisprudential or otherwise restricted significance and incorporation of such terms into the legislation would entail their interpretation in accordance with the accepted jurisprudential or otherwise restricted meaning. If it is intended that a term or concept should have only a restricted meaning or application, appropriate language must be used by the draftsman to give effect to such intent. In some countries judicial decisions and statutes dealing with interpretation are relevant in determining the meaning to be attributed to a particular term or expression. For instance, the meaning of the term "possession" in drug statutes has been an area of controversy in many countries with several conflicting judicial decisions. Sometimes, the general rules of interpretation are incorporated in a special statute, such as the Interpretation Ordinance No. 21 of 1901 of Sri Lanka. Such statutes will normally apply when other statutes need to be interpreted, unless it is expressly stated or the context makes it clear that a different interpretation was intended or that the general rules of interpretation are not applicable.

The definitions of various concepts and terms relating to drugs that have been formulated by WHO expert committees and at WHO consultations have been set out in a number of publications and documents. Over the years, several countries have adopted some of these definitions, while others have used them with appropriate modifications. National legislation, too, provides a range of similar definitions. Unless there is a movement towards the harmonization of national laws, no standard or model definitions need to be formulated. Each country must be left to identify the definitions most appropriate for its own legislative purpose.

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CHAPTER 7

Institutional mechanisms for the regulation of pharmaceuticals

In any branch of the health sector there has to be a central point or points from which the more important administrative and operational activities are directed. In the area of drug legislation, different countries have provided for a variety of authorities and mechanisms to give effect to the legislative scheme.

The nature and structure of the institutional mechanisms to be established is a matter for national authorities to decide. There is no standard model to suit all situations. This chapter looks at some of the issues that are relevant to the task of developing the institutional mechanism or mechanisms to be built into a national law on pharmaceuticals.

Before deciding on the nature and structure of the institutional mechanisms, it is necessary to compile an inventory of the powers, duties, and responsibilities required to give effect to the different legislative provisions that are contemplated, with a view to ascertaining the possible authorities and mechanisms among which they should be shared.

The nature of the allocation or assignment of powers, duties, and responsibilities can be illustrated by a few country case studies. Under the Cosmetics, Devices, and Drugs Act of Sri Lanka (Act No. 27 of 1980) the Director of Health Services, an office that had existed in the Ministry of Health long before the legislation was enacted, is designated as the “Cosmetics, Devices, and Drugs Authority”.

In terms of the legislative scheme, the Director is the repository of a multitude of powers, duties, and responsibilities. For instance, no one may manufacture, import, sell or distribute, or offer for sale any drug without a licence issued by the Director. Any premises where drugs are manufactured, prepared, stored, or sold have to be licensed by him. Moreover, the law requires every drug to be registered. In order to facilitate the implementation of the Act, provision is made for the establishment of an advisory committee known as the Cosmetics, Devices and Drugs Technical Advisory Committee. The Chairman of this 15-member Committee is the Director of Health Services. The legislative scheme also provides for:

(a) an Assistant-Director of Health Services in charge of Cosmetics, Devices and Drugs Control Administration (ex officio secretary of the Advisory Committee);
(b) subcommittees of the Cosmetics, Devices and Drugs Technical Advisory Committee;
(c) any person (by name or office) to whom the Director has, with the prior approval of the Minister, delegated all or any of his powers;
(d) authorized officers (any Superintendent of Health Services, Medical Officer of Health, Public Health Inspector, Food and Drugs Inspector, or Drugs Inspector appointed by the Minister); and
(e) approved analysts (the Government Analyst and others appointed by the Minister as additional approved analysts).

A slightly different approach has been adopted in Nepal. The Drugs Act — Act No. 21 of 2035 (1978) — stipulates that: “His Majesty’s Government shall constitute a Department of Drugs Administration for the purpose of carrying out the objectives of this Act” (section 5).

The Department of Drugs Administration is responsible for a multitude of functions, such as recommending the establishment of drug manufacturing industries and registering drugs. The powers of the head of the department can be delegated to any official. In addition to the establishment of this Department, the Drugs Act provides for two mechanisms, namely, the Drugs Consultative Committee and the Drugs Advisory Committee.

The former has to advise the Government on policy and administrative matters relating to drugs (section 3 of the Act), while the latter has “to advise the Department [of Drugs Administration] on the technical matters in relation to research, development and control of drugs” (section 4 of the Act). The Royal Drug Research Laboratory has been designated as “the principal organ of the Government for the scientific research, testing and analysis of drugs” (section 6 of the Act). The Act also provides for drug inspectors and analysts.

The legislative scheme adopted by Mali in 1981 is different from the two schemes described above. The Malian Office of Pharmacy was required by law to establish the following divisions:

(a) a Supply Division;
(b) an Inspection of Medicaments Division;
(c) a Traditional Medicines Division; and
(d) a Products Division.

In addition to these divisions, the legislative scheme envisages two centres, the Pharmaceutical Production Centre and the Traditional Pharmacopoeia and Medicine Centre. The entire range of relevant activities comes under the authority of these divisions and centres attached to the Office of Pharmacy. Simple preparations are produced by the Pharmaceutical Production Centre.

Whatever the nature of the mechanism that it is finally decided should be built into the legislation, it is important to note that specific

1 Law No. 81-18 of 27 March 1981 and Decree No. 84 PG-RM of 9 April 1981.
powers, duties, and responsibilities must be clearly delineated. If there is to be more than one functionary or mechanism, there must be a clear demarcation of powers, duties, and responsibilities.

It is infrequent for legislative provision to be made delineating the functions and duties of an official functionary such as the secretary or director of health services. Barbados is one country that has prescribed the functions of the Director of the Drug Service. The Drug Service Act of 1980 (Act No. 58), whereby a Drug Service Office was established, states that the functions of the Director are to: (a) oversee the storage and distribution of drugs and related items; and (b) ensure that, as far as practicable, an adequate stock of drugs is available at all times for the purposes of the drug service at a reasonable price.

If a particular responsibility is assigned by statute to the holder of an office or to an agency, it is solely that office or agency that has to discharge the responsibility so assigned. Under the Barbados law, the Director is responsible for the collation of the information and data enabling him to assess needs and to ensure that adequate stocks are available to meet such needs. It is also his responsibility to ensure that drugs are reasonably priced. If the principal responsibilities are set out in clear and concise terms in the law it facilitates accountability and follow-up action.

Coordination is another issue to which policy-makers and legal draftsmen must address themselves.

In some countries, there is a multiplicity of statutory functionaries and institutional mechanisms. For example, the recent Drugs Control Ordinance1 of Bangladesh provides for: (a) a Licensing Authority; (b) a Drug Control Committee; and (c) a National Drug Advisory Council.

The Licensing Authority is entrusted with functions such as: the registration of medicines and the cancellation or suspension of such registration; approving the importation of drugs and pharmaceutical raw material; and approving the text of advertisements. On matters of registration and cancellation, this Authority has to act on the recommendations of the Drug Control Committee. The Committee — the composition of which has not been laid down in the Ordinance — has to evaluate the safety, efficacy, and usefulness of medicines. The National Drug Advisory Council has to advise the Government on:

(a) measures required for the implementation of the national drug policy that may be adopted by the Government;

(b) measures for the promotion of local pharmaceutical industries and the production and supply of essential drugs to meet the needs of the country;

(c) matters relating to the import of drugs and pharmaceutical raw materials;

(d) measures for the coordination of the activities of various ministries, agencies, and persons dealing with the manufacture, import, distribution, and sale of drugs.

1 Ordinance No. VIII of 1982.
The Ordinance also envisages that the Government shall exercise certain functions. For instance, the responsibility for fixing the maximum price of drugs and imported pharmaceutical raw materials is assigned to the Government. The Government can also review any licensing agreement between a Bangladeshi concern and a foreign concern for manufacturing drugs in Bangladesh, and if any provision in the agreement is contrary to the national interest it can direct the concern to modify the provisions. Failure to comply with a Government direction may result in the cancellation of the manufacturing licence.

A multiplicity of committees and large representation on such committees will not necessarily guarantee quicker or better results. When statutory powers and duties are distributed between a multiplicity of agencies and functionaries, as in the case of Bangladesh, there is a need to provide for mechanisms to ensure coordination and interaction so as to achieve optimum operational effectiveness and to eliminate red tape and bottle-necks in the administrative process and channels of communication. It is advisable to spell out in the legislation the specific ways in which such coordination and interaction can take place. Taking the Bangladeshi legal structure described in the preceding paragraph as an example, there are a number of possibilities available to the draftsman to establish linkages and to strengthen areas of coordination and interaction. More specifically, the following possibilities can be identified:

(a) the Licensing Authority and one or more members of the Drug Control Committee to be ex officio members of the National Drug Advisory Council;

(b) the National Drug Advisory Council to be under a mandate to monitor the implementation of national drug policies and to advise the Government on policy changes;

(c) the Minister, on the recommendations of the National Drug Advisory Council, to issue general or special directions to the Licensing Authority on the importation of drugs and pharmaceutical raw materials, pricing formulae, etc.;

(d) the power to "suspend" registration to be acted on by the Licensing Authority only on the recommendation of the Drug Control Committee, as in the case of granting or cancelling registration.

The question of coordination and follow-up is important even in relation to the establishment of committees and subcommittees. Some countries provide for a large representation on committees to obviate the need to set up several subcommittees. However, there are disadvantages in having very large committees.

Legal provisions relating to institutional mechanisms must, in addition to defining powers, duties and responsibilities, specify how the members are to be appointed and removed, the number of members constituting a quorum for valid meetings, and the procedures to be followed at meetings for the transaction of business. These are matters to be laid down in regulations or by-laws or even in circulars. Some matters regarding
procedure may be left to be determined by the members at their first
meeting.

Countries with a federal system of government might have to con-
sider the necessity for a central mechanism in addition to regional or
provincial mechanisms. Constitutional requirements determine the need
for a multiplicity of mechanisms and the distribution of powers, duties,
and responsibilities. Under the Drugs Act of Pakistan,¹ for instance,
there is a Central Licensing Board and an Appellate Board, both consisting
of representatives of the Federal Government and the provincial govern-
ments. The Act requires every provincial government to appoint a Pro-
vincial Quality Control Board. There is also provision for the establish-
ment of federal as well as provincial drug laboratories and for the appoint-
ment of analysts and inspectors. An important provision in the Act, in the
context of the federal structure of government, is the one that empowers
the Federal Government to issue directions. Section 13 reads as fol-
low:

The Federal Government may give such directions to a Provincial Government as may
appear to the Federal Government to be necessary for carrying into execution in the
Province of any of the provisions of this Act or of any rule or order made thereunder or
for maintaining supplies of drugs of standard quality at reasonable prices or for the
achievement of uniformity in respect of any matter in different parts of Pakistan.

The exact location of the institutional mechanism in the governmen-
tal structure is a matter to be determined by national authorities. In most
countries it is located in the department or ministry responsible for the
health of the people — “an arrangement [that] permits the agency to work
closely with the planning, organization and delivery of health care”.² The
minister or the head of the department or ministry is usually the person
who is empowered to make appointments of functionaries, personnel,
members of boards, etc. However, there are exceptions. For instance, in
1981 Ethiopia enacted a Proclamation³ for the establishment of a Phar-
maceuticals and Medical Supplies Corporation with the Minister of
Health as the Chairman of the Board of Management. The establishment
and operation of pharmacies and medicament stores and the conducting of
research to promote the development of pharmaceutical preparations and
medical supplies are functions of the Corporation. Whatever the exact
location of the institutional mechanism, it is necessary to ensure that all
relevant government departments and agencies and the key professional
groups⁴ have representation on it.

¹ Act No. XXXI of 1976.
² Guidelines for the development of a national drug control program. Unpublished
document (no date) of the Pan American Health Organization, Washington, DC, p. 37.
³ Proclamation No. 207 of 23 May 1981.
⁴ The recent Medicines Act of the Gambia, Act No. 2 of 1984, provides, for instance, for
a person elected by the Gambian Medical and Dental Association to serve on the Medicines
Board.
Rationalization of the availability of pharmaceuticals

This chapter describes some of the special strategies that are available for regulating the number of pharmaceuticals available on the market. The strategies discussed here are those that are either based on or directly related to policy decisions aimed at "rationalizing" the availability and use of drugs. Drugs may reach the market either through import or through manufacture; in a few developing countries both sources are used. The discussion of the different strategies for regulation set out here is not comprehensive and needs to be supplemented by the subsequent chapters dealing with such aspects as registration, import, and manufacture.

Essential Drugs

The concept of "essential drugs" has gained considerable currency since the mid-1970s when it was first propounded by WHO. The rationale underlying this concept was set out, in 1977, by the WHO Expert Committee on the Selection of Essential Drugs, in the following terms:

for the optimal use of limited financial resources the available drugs must be restricted to those proven to be therapeutically effective, to have acceptable safety and to satisfy the health needs of the population. The selected drugs are here called "essential" drugs, indicating that they are of the utmost importance, and are basic, indispensable and necessary for the health needs of the population.

The preparation of lists of essential drugs has many advantages. It has been pointed out that "such lists of drugs can provide:

(a) an avenue to improve the quality of drug utilization and management;
(b) an approach to change the cultural conception of health and the role of drugs;

(c) common baselines for the training programmes of the medical profession and health-care operators;
(d) a tool for more integrated health-need oriented drug research;
(e) help and stimulus for the development of indigenous drug industries;
(f) an easy reference parameter for drug surveillance and information programmes; and
(g) improved indices of drug economy (optimization of accessibility, management, procurement, production, distribution, storage and usage)."'

Different countries require different kinds of drugs. The requirements depend on many conditions such as:

(a) the pattern of prevalent diseases;
(b) the type of health personnel available;
(c) financial resources;
(d) genetic, demographic, educational, and environmental factors;
(e) physical facilities for distribution and storage; and
(f) possibilities of easy and prompt procurement.

For this reason, it is neither practicable nor feasible to have any kind of uniform list applicable to all countries. What is possible, however, is to prepare a model or guiding list of essential drugs, on the basis of which countries can determine the minimum number of drugs they require. These lists need to be periodically reviewed and drugs added to or deleted from them, as necessary.

Essential drug lists have been accorded legislative or official sanction in several countries. In Niger, an Order was made in 1981\(^2\) prescribing some 80 medicaments to be ordered by district medical services and dispensaries. Only departmental directors of health are entitled to include drugs other than those listed in the Order. By another Order of the same date,\(^3\) the number of drugs to be ordered by hospitals was restricted to 210. Any other drug may be ordered provided the chief physician of the establishment is able to justify the need for it. The final decision is with the Office of the Secretary-General of the Ministry of Public Health and Social Affairs.

The concept of essential drugs can be referred to in the main legislative text with the list reproduced in the form of a regulation. Another possible approach is to list the essential drugs in a national formulary (or a similar text) to which reference can be made in the main legislative text.

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2 Order No. 014/MSP/AS of 6 July 1981.
National Formulary

The listing of drugs in a national formulary enables the importation and manufacture of drugs to be confined to those that are listed, if appropriate legal provision is made for this purpose. For instance, Peru has a long tradition of rationalizing the availability of drugs by this method. In this context, it is of interest to examine briefly the provisions of a more recent Peruvian decree, enacted in 1979, dealing with basic medicaments in the health sector. “Basic medicaments” have been defined as those reasonably priced pharmaceutical products of guaranteed quality that have been approved by the Ministry of Health, are intended to facilitate health promotion, protection, and restoration activities, and are listed in the Official Formulary of Basic Medicaments in the Health Sector. The decree requires the Ministry of Health, the Peruvian Social Insurance Scheme, public welfare agencies, the National Institute for the Care and Promotion of Minors and the Family, local authorities, public agencies and undertakings, and similar bodies to prescribe and use only basic medicaments. These institutions are prohibited from acquiring, prescribing, or selling other products having a similar pharmacological action to those listed in the Official Formulary, with certain exceptions.

In Guatemala, by an Order made in 1979, the National Therapeutic Formulary has been declared to be the definitive text prescribing the pharmaceutical products to be used in national hospitals, health centres, and health posts of the Ministry of Public Health and Social Welfare. Proposals for revisions and updating are considered by a multidisciplinary Committee on the Therapeutic Formulary. The Committee is required, inter alia, to carry out an economic and administrative analysis in order to determine whether the Formulary already contains a cheaper product having similar therapeutic value. Medicaments identified as being the most effective and safest for the treatment of a specific disease must be accorded priority for inclusion in the Formulary. The Committee is required to make a periodic analysis of morbidity statistics to determine whether the priorities should be changed.

The periodic review of a formulary and its updating can be treated as an administrative function, though this function can be assigned in a legal instrument to a particular agency. Appropriate criteria need to be developed for the revision of the formulary.

Once a formulary has been accorded legislative sanction, either by its incorporation in a regulation or by reference to it in the main text or in the regulations, it forms the basis for the regulation of importation, manufacture, and use of drugs. A formulary facilitates long-term planning and programming by health administrators, drug importers, and manufacturers. In addition to a national formulary, it is possible to prepare a local formulary for a group of medical institutions, health centres, etc.

2 Order No. SP-M-12-79 of 7 March 1979.
Multidimensional Strategy

The availability of drugs can be restricted by a mix of strategies rather than a single method. In the past, most drugs laws provided for one or two methods, such as registration or import restrictions, but present trends in some countries indicate a move towards viewing the problem from a broad perspective with intervention at several different points.

In the case of Bangladesh, the availability of drugs was restricted in 1982 by the adoption of five modalities:¹

1. The legislation stipulated that no medicine of any kind could be manufactured for sale or be imported, distributed, or sold unless it had been registered with the Licensing Authority. The Authority had to act on the recommendations of the Drug Control Committee.

2. Certain medicines, listed in three schedules, were subject to special restrictions, which were to become operative within a stipulated time-limit. Medicines specified in Schedule I had to be destroyed, while Schedule II medicines had to be registered after changes in their formulation as directed by the Licensing Authority. Non-registration meant that these medicines could neither be manufactured nor sold. Schedule III comprised a list of drugs that could neither be manufactured nor imported, thus resulting in a complete withdrawal of such drugs from the market. A fourth Schedule was introduced subsequently in the form of an amendment to the Ordinance.² Unless the medicines in this Schedule were registered, it was not possible to manufacture, distribute, or sell them.

3. The legislation did not permit a drug to be manufactured locally, under licence granted by a foreign company that had no manufacturing plant in Bangladesh, if the drug or a substitute was already being produced in Bangladesh.

4. The legislation required the prior approval of the Licensing Authority for the importation of pharmaceutical raw materials.

5. The government was empowered to review any licensing agreement between a Bangladeshi concern and a foreign concern for the manufacture of any drug in Bangladesh and to give directions for modifying the agreement. In the event of non-compliance with any direction, the manufacturing licence could be cancelled.

The different methods of registration, import restrictions, manufacturing restrictions, etc. are discussed in greater detail in subsequent chapters. The Bangladeshi example highlights the fact that a country has a range of choices open to it and that various modalities can be used to formulate an appropriate strategy.

¹ Ordinance No. VIII of 1982.
² Ordinance No. XXVIII of 1982.
CHAPTER 9

Legal controls in respect of importation, manufacture, and exportation of pharmaceuticals

The legal controls in respect of the importation of pharmaceuticals are of paramount importance to most developing countries, which generally do not have the resources necessary to establish manufacturing plants. However, some developing countries are now building up their manufacturing capacities, albeit on a modest scale, and a few countries have already begun to export drugs. This chapter thus deals with the legal controls that may be imposed on imports and with the legal framework relating to manufacture and exportation.

Importation Systems

Categories of importation system

State practices and laws relating to importation fall into two broad categories:

(a) Liberal unrestricted import of virtually any drug

In some countries, it is possible to import freely any pharmaceutical with the exception of those that are banned; such a situation leaves much to be desired. First, drugs that are unsafe and of inferior quality can infiltrate into the market. Second, scarce foreign exchange is spent on importing drugs that may be of doubtful therapeutic value. Third, a policy for the rational distribution and use of drugs cannot be formulated unless there is a system whereby the drugs coming into the country can be easily monitored. Finally, unrestricted importation is a disincentive for the promotion of the domestic manufacture of drugs.

Many countries are moving away from this situation by developing appropriate controls. These controls are discussed more fully below and in Chapter 10.
(b) Imports confined to drugs that are registered, approved, licensed, or similarly controlled

In restructuring the drug supply system of any country two objectives are of paramount importance:

(i) to rationalize the national supply system in accordance with the essential drugs concept (see Chapter 8); and
(ii) to ensure that only drugs of acceptable quality, safety, and efficacy are available.

By regulating the inflow of drugs by means of appropriate controls and checks, both these objectives can be achieved. The commonly used controls and checks, which take the form of registration, approval, or licensing of the drug, are described more fully in Chapter 10.

Licensing of importers

While importation systems fall into the two broad categories referred to above, it should be noted that the licensing of importers is as important as the control of the drugs imported. Importation systems and importers differ not only from country to country but also from product to product.

There are a few countries that have a state monopoly in respect of imports of pharmaceuticals. No private sector establishments or individuals are permitted to import drugs, with the possible exception of medical practitioners who may be allowed, in urgent and exceptional circumstances, to import a rare drug for a specific disease.

Political and trade ideologies often call for monopolies in favour of the state or of a particular agency, which can be granted by legislation. The types of drug to be imported and the sources from which drugs are to be obtained will then be determined by that body. For instance, in 1969, an Ordinance\(^1\) was enacted in Algeria vesting in the Algerian Central Pharmacy the exclusive right to import pharmaceutical products. The importation of drugs being centralized or being entrusted to a state agency should not in any way be permitted to result in a relaxation of quality assurance. Drug control inspectors, for instance, should verify the quality of drugs even though they have been imported by the state.

There are several cost-benefit and cost-effectiveness factors that have to be taken into account before deciding to establish a monopoly in respect of drug imports. Drug procurement systems need to be carefully devised, with regard to possible suppliers and import facilities. Moreover, if drug procurement is to be centralized, adequate storage facilities and distribution networks need to be set up.

In most countries, there are authorized or licensed importers who are permitted to import pharmaceuticals, either exclusively or along with a state department or agency.

\(^1\) Ordinance No. 69-14 of 25 March 1969.
Licensing systems for imports

In some countries, the system of licensing is inextricably interwoven with the registration process, which is described in Chapter 10. In others, the licensing system is part of a general trade policy not specifically geared to the elimination of unsafe or inferior products.

An import licence is usually granted for (a) the import of a particular drug; or (b) the import of a particular category of drugs. Generally, the importer must be a person who has been licensed to sell drugs, either as a retailer or as a wholesaler. Certain laws provide for direct importation by medical practitioners for their professional and individual needs. Licences to import drugs other than in a finished form, or in small quantities specifically for the purposes of clinical trials and experimentation, are also issued.

Countries differ in the requirements and conditions for the granting of licences. If there is a single manufacturer for several products, a single licence may be issued covering all those products. The duration of the validity of licences varies from country to country. The place of entry for imports can be specified either in the regulations or in the licence. For instance, the Indian regulations specify different cities as entry-points, depending on whether the drugs are imported by air, sea, or rail. Land-locked countries and those with common borders need to restrict the number of points of entry. Otherwise, it would be virtually impossible to conduct any analysis of samples of drugs or maintain surveillance over drugs entering the territory. Smuggling of drugs is difficult to eliminate and enforcement authorities have to be authorized to seize any consignments that people try to import into the territory other than through an authorized entry-point.

The conditions to be attached to a licence vary depending on whether the drugs are to be imported in the manufacturer's original packing or not. Domestic repacking necessitates adherence to certain standards, both in relation to the premises where such repacking is to be done and to the technical competence of the personnel. To permit the verification of quality at the time of import it is essential that there should be proper storage facilities and expeditious methods of analysis and reporting. An importer should be legally obliged to provide samples together with supporting documents. Whether a sample from every batch needs to be verified is a matter to be decided by the regulatory authorities, having regard to the nature of the drug and the documentation already available.

After clearance from the customs house or other specified place, drugs need to be properly stored; many countries provide for the licensing of premises that are to be used for storage purposes. Regulatory authorities should have access to such premises at all reasonable times to enable them to carry out investigations regarding the conditions of storage and the adequacy of storage facilities. Labelling of imported drugs is another matter that needs to be regulated. Chapter 12 deals more fully with this

1 Drugs and Cosmetics Rules, 1945.
aspect. Records of the utilization and distribution of drugs should be made available on request. Such records are useful for improving existing systems of procurement and distribution.

The implementation of a law on pharmaceuticals entails considerable expenditure. For that reason, many laws provide for a fee to be levied as a precondition for the issuing of a licence. Fees are sometimes collected for inspection and analysis as well, though this practice is not universal. The fees collected can be used to cover the administrative expenses of enforcing the law.

Import prohibitions

Different countries have identified different grounds for the prohibition of the importation or marketing of pharmaceuticals. For instance, in Bahrain the Medicaments Commission is entitled to recommend to the Ministry of Health that a particular pharmaceutical product should not be imported or marketed on the ground that it is "harmful to public health".\(^1\) Other grounds for prohibition are more specific: for example, the Minister, acting on the recommendation of the Medicament Control and Pharmacy Division, can suspend the importation of a registered medicament or a pharmaceutical product if its price exceeds the limits accepted in neighbouring Arab countries.\(^1\) Recent legislative changes in India\(^2\) provide for several grounds for banning the import, manufacture, or sale of a drug. The Central Government has been empowered to prohibit the import, manufacture, sale and distribution of a drug if it is satisfied that it is necessary or expedient to do so in the public interest because \((a)\) the use of the drug is likely to involve a risk to human beings or animals; or \((b)\) the drug does not have the therapeutic value claimed for it or contains ingredients for which there is no therapeutic justification.

Manufacture

Introduction

Different countries obviously have different levels of manufacturing capability for pharmaceutical products.\(^3\) At the present time, there are countries where \((a)\) there is no pharmaceutical industry; \((b)\) some packaging and formulation is carried out; \((c)\) a substantial number of essential drugs are formulated locally; or \((d)\) drugs are produced on a large scale from raw materials and basic chemicals.

\(^1\) Decree-Law No. 26 of 1975.
\(^2\) Act No. 68 of 1982.
The experience gained by some countries in the production of drugs is illustrative of the problems of, and prospects for, large-scale domestic production.\(^1\)

The establishment of a local formulation capability has many advantages to offer:\(^2\)

\(a\) it facilitates the regular and sufficient availability of essential drugs of internationally acceptable quality, thus making possible the provision of health care at reasonable cost;  
\(b\) it permits flexibility of drug supply corresponding to local needs, including sudden epidemics and other emergencies;  
\(c\) it optimizes the use of the limited available financial resources, especially hard currency, for drug procurement;  
\(d\) it creates local employment opportunities and strengthens manpower development throughout the spectrum of activities related to the pharmaceutical industry;  
\(e\) it creates a multiplier effect on supporting industries; and  
\(f\) it generates the social, technological, and economic benefits associated with the existence of a viable industry.

It has been said that a national drug industry “can also have considerable strategic value during times of war, trade embargo, epidemic or other national disaster, when the health of large numbers of people is endangered”.\(^3\)

National aspirations in this regard are understandable, but developing countries interested in undertaking local production should take into account the following factors:

1) Feasibility studies for local industries must be comprehensive and realistic, taking into account the chances of successful transfer of technology and overcoming local problems, including finance (external and domestic).

2) Command of technology is only one factor — managerial maturity and skills are just as important.

3) The local market does not always have the capacity and willingness to absorb the planned production. The public sector of the home market often operates on limited budgets, while on the private market domestic products are at a disadvantage compared with imported goods.

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(4) Exports to neighbouring countries can be expected only if there is a demand and if prices and quality compare favourably with those of drugs from other sources. This requires rationalization of production to fill needs within economic zones of cooperation rather than producing identical items. This applies especially to drugs that are easy to formulate.

Local pharmaceutical plants have a role to play in the production of essential drugs on a large scale for primary health care. The feasibility of establishing production facilities for such drugs in developing countries should be evaluated within the socioeconomic context for each country.

Good manufacturing practices

At the Twenty-eighth World Health Assembly in 1975 the revised text of *Good practices in the manufacture and quality control of drugs* (commonly referred to as GMP) was adopted.\(^1\) It was recommended that Member States should apply these requirements.

The practices laid down in GMP (see Annex 2) are designed to ensure that the drugs received by the consumer have been subjected to stringent controls from the beginning to the end of the manufacturing cycle to ensure that they are of high quality. The expression “manufacturing” for this purpose refers to all operations involved in the production of a drug, including processing, compounding, formulating, filling, packaging, and labelling.

The requirements set forth in GMP are intended to apply primarily to preparations for human administration. However, this should not detract from the need for similar quality considerations in the manufacture of veterinary preparations. The requirements represent general guides stipulating minimum standards. They are not designed to replace other legal controls, but rather to complement or supplement them.

Licensing

Manufacturing licences may be of different types. For instance, in Pakistan\(^2\) the following types of licence are issued:

- licence to manufacture by way of basic manufacture;
- licence to manufacture by way of semibasic manufacture;
- licence to manufacture by way of formulation;
- licence to manufacture by way of repacking; and
- licence to manufacture for experimental purposes.

National regulatory authorities need to be empowered to regulate the use of certain substances — chemicals, colorants, etc. — in the manufacture of drugs. Although such substances are not likely to be very numerous

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\(^1\) Resolution WHA 28. 65.
it is advisable that the authorities should be vested with that power. The Colombian legislation\(^1\) regulating the registration of medicaments, for instance, states that the Ministry of Public Health can determine the substances that may not be used in the manufacture of products such as medicaments in view of their toxicity, undesirable side-effects, or the existence of scientific evidence that they have no therapeutic effect.

Effective monitoring of manufacturing practices depends as much on the frequency of checking as on what aspects are checked. In India, regulations require drug inspectors to visit manufacturing establishments at least twice a year.\(^2\) In Brazil, a detailed checklist for inspectors has been prescribed.\(^3\) The range of matters that should be scrutinized is very wide, as the following main headings show: administration and general information; storage premises; water installation; reception and storage of raw material; reception and storage of packaging material; returned and/or recalled products; weighing area; premises for storage of finished products; quality control; production; production area; organization; drug products; injectable products; liquid products; packaging; labelling.

Supervision by outsiders, such as drug or quality control inspectors, is not an adequate substitute for the responsibility of the manufacturing industry to ensure that high standards are maintained consistently and that there is adequate supervision to ensure that there are no deviations from such standards. GMP provides for qualified personnel, quality control departments, quality control laboratories, and self-inspection. These or similar requirements can be incorporated into regulations governing the manufacture of drugs. No manufacturer should release drugs that do not conform to accepted standards. Standards or quality specifications can be laid down as a condition of the manufacturing licence. Appropriate legal provisions allow the suspension or cancellation of a manufacturing licence if stipulated standards or specifications are not complied with. Specification of quality or standard as a condition in the licence is feasible only if the manufacturer is producing a limited number of drugs. If there is a wide range of products, it is much better to impose a general condition requiring compliance with quality specifications.

In addition to making provision for inspection and quality verification as a regular in-plant procedure, manufacturers should be required to retain a sample of each lot or batch of a packaged drug for a prescribed period. The duration of the period to be prescribed will vary according to the particular drug.

There are various methods of giving legal sanction to the principles set out in the GMP text. For instance, the main statute can refer to the text, which may then be reproduced in the form of a schedule to the main statute. Another method is to reproduce the text as a regulation or order. Alternatively, it would be possible to make the manufacturing licence

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1\( \text{Decree No. 281 of 21 February 1975.} \)
2\( \text{Ordinance No. 69-14 of 25 March 1969.} \)
3\( \text{Order No. 14 of 8 October 1981.} \)
subject to the standards, conditions, and requirements set out in the text, with appropriate modifications, if deemed necessary. What is important is that the standards, conditions, and requirements should have a valid basis in law so that in the event of any deviation or departure, appropriate legal action can be taken against the manufacturer. The text of the GMP may have to be adapted to suit local conditions. For instance, the recent regulations of Chile\(^1\) on the National System for the Control of Pharmaceutical Products, Foods for Special Dietary Uses and Cosmetics not only prescribe the duties of the technical director and the chief of the quality inspection department of manufacturing laboratories, but also make it mandatory for the owner of the establishment to provide these officers with the equipment and instruments they need to enable them to determine the quality, potency, purity, and stability of raw materials and manufactured products. Under the Indian legislation\(^2\) any machinery used for the manufacture of a misbranded, adulterated, or spurious drug in respect of which a person has been convicted is liable to confiscation, as are all stocks, containers, packages, and coverings.

**Restrictions on manufacture**

A consequence of the prior screening of applications for the manufacture of drugs is that permits to manufacture can be restricted to drugs for which there is a genuine local demand. In Ecuador,\(^3\) all companies manufacturing medicaments are required to produce at least two medicaments for the Basic Social Medicaments Programme of the Ministry of Public Health in accordance with the list issued by the Ministry.

**Export**

Drugs are exported by only a few countries. Consequently, legal controls are still in their formative stages. However, it should be noted that if a country participating as an exporter in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (see Annex 3) permits the export of drugs, it is required to take various measures designed to ensure the quality, safety, and efficacy of the drugs (for further details, see Chapter 10).

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2. Act No. 23 of 1940.
Strategies for the assurance of drug quality, safety, and efficacy

This chapter is in two parts. The first part discusses national registration procedures and the application of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. It also considers the mechanics of information dissemination as a possible means of providing some guarantee about the quality, safety, and efficacy of pharmaceuticals. The second part deals with issues that are important in drafting and implementing legislation relating to quality assessment and assurance.

Registration, Certification, and Information Dissemination

Registration

Licensing of the import or distribution of drugs can be either independent of the process known as “registration” or based on it. Ideally, registration should precede licensing since the process of evaluating a drug with a view to registration should preferably involve consideration of its safety and efficacy, and any decision to import or distribute a drug should be based on the results of such evaluation. The mechanics of registering drugs and the infrastructure and resources required for purposes of evaluation are complex. Not surprisingly, therefore, some countries have only a system of licensing. In the absence of a system of registration, licensing tends to be based on ad hoc decision-making processes, which are often geared to general trade policies and the availability of foreign exchange for financing imports. Until such time as registration procedures are set in motion, a licensing system in respect of import and distribution serves a dual function — first, it permits the regulation of drugs that are being imported and distributed, although the basis of regulation may not be as sound or systematic as in a situation where there is a registration system; and, second, it facilitates the monitoring of the drugs that are available on the market.

Just as licensing can be independent of registration, it is also possible to have a registration system without a licensing system, in which case
mere proof of registration, evidenced by a certificate of registration is considered to be sufficient for purposes of import and distribution. The expressions “certificate”, “licence”, and “registration” can cause confusion unless they are used in relation to a particular national context.

The complexity of launching a registration system was pointed out at the WHO Consultation on Basic Elements of Drug Legislation and Regulatory Control for Developing Countries, held in 1981.\(^1\) The Consultation concluded that over-ambitious attempts to introduce simultaneously a number of new regulations and rules with regard to drug registration procedures often failed because the manpower necessary to enforce them had been underestimated.

Different countries have different authorities and agencies entrusted with the responsibility of reviewing applications and registering drugs that receive favourable consideration. In Algeria, for instance, the responsibility for drug registration rests with the Ministry of Public Health but applications are reviewed by the Central Registration Committee (Commission centrale de la Nomenclature). In Pakistan, registration is a responsibility of the Federal Government and is carried out by the Registration Board headed by the Director-General of Health. Once a drug has been registered, the Board must notify all the provincial governments. The legislation\(^2\) requires provincial governments to take all necessary steps to ensure compliance with the conditions subject to which a drug is registered and to prevent the manufacture or sale of a drug that has not been registered or the registration of which has been suspended or cancelled.

Registration requirements generally apply in respect of all drugs. The information usually sought can be classified into two broad categories: (1) administrative data; and (2) pharmaceutical, pharmacological, toxicological, therapeutic, and clinical data.

The first category includes information relating to such matters as the name of the product and details of the manufacturer; the status of the product in the country of origin and other countries; and the content of labelling and advertising material. The second category comprises detailed information of a technical nature.

The documentation required and the criteria for accepting or rejecting an application for registration vary from country to country. Considerations of space do not permit a detailed survey of these matters.\(^3\) It has often been argued on behalf of manufacturers that inasmuch as the purpose of drug registration is “to ensure that the patient receives drugs which are of the required quality and which have been adequately tested and evaluated for safety and efficacy for their intended use... authorities


\(^2\) Drugs Act No. XXXI of 1976.

\(^3\) For a survey of more than 25 developing countries, see: INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS ASSOCIATIONS. Legal and practical requirements for the registration of drugs (medicinal products) for human use. Zurich, IFPMA, 1980.
should limit their registration requirements for a product to considerations of safety, quality and efficacy. However, additional criteria are being applied by various countries. Some of these are:

(a) price;
(b) comparative therapeutic and/or safety advantages;
(c) local manufacture of a similar product;
(d) the availability on the market of several products with the same active ingredient;
(e) combinations not offering an advantage over individual products; and
(f) therapeutic justification and medical need.

From the point of view of developing countries each one of the above criteria has some merit. It has been claimed, for instance, that the use of price and relative efficacy as criteria for the registration of a new drug has the following advantages:

1. If a government is given the authority to negotiate the selling price of the drug prior to registration, it will undoubtedly arrive at a lower price than if the manufacturer is permitted to establish his own selling price. Thus, savings will result at both the government and consumer levels.
2. The less efficacious drugs will not be likely to reach the market, which will result in improved drug therapy.
3. The total number of drugs on the market will be reduced, resulting in a reduction in the cost of control or an increase in the effectiveness of the control. Within certain limits, government expenditure for the control of drugs will be proportional to the number of pharmaceutical products that have to be examined.
4. Drug manufacturers will be encouraged to concentrate their research and development efforts on significant improvements in therapy rather than on drugs that offer only minor advantages over drugs currently available.

The period for which a drug is registered varies from country to country. Some countries fix a mandatory period within which the registered product should be marketed. Renewal of the registration can also be conditional on the product being marketed. The fees levied for the first registration as well as those for renewals may be the same for all drugs or may vary with the category in which the drugs fall. These fees may be used to cover some or all of the expenses of the regulatory agency.

The legislative instrument relating to the registration of products may provide for the imposition of various conditions for registration; for

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1 From the IFPMA survey (footnote 3, p. 52), p. xvi.
2 An example that is often cited is the Norwegian legislation of 1964 (section 14). See also the Medicines Act of the Gambia, No. 2 of 1984.
instance, (1) WHO-type certificates for imported drugs, and (2) information on the reporting of side-effects, withdrawal of the product from other countries, etc. It may be noted that the WHO certification scheme on the quality of pharmaceutical products moving in international commerce lays down that both importing and exporting countries have to notify new defects of a serious nature not attributable to local conditions and circumstances (see Annex 3). As part of the conditions to be attached to registration, changes in the package insert or in the text of advertisements, for instance, can be subject to prior approval. Furthermore, changes in trade marks may be accepted only if the registration is amended or an altogether new application is made.

The registration of drug combinations may be permitted subject to certain additional conditions or qualifications.

There may well be situations where, for urgent reasons, a departure from the prescribed registration and licensing procedures may be warranted. Some laws therefore provide for a system of “emergency licences”.

Developing countries have prescribed different grounds on which the registration of a drug or the licence for marketing can be withdrawn. For instance, in Kenya, a certificate may be suspended or revoked if, for example:

- the premises on which, or on part of which, drugs are manufactured, assembled, or stored by or on behalf of the holder of the certificate of registration are unsuitable for the manufacturing, assembling, or storage of drugs; or
- new information has been discovered by the Pharmacy and Poisons Board that indicates that the drug is unsafe or dangerous.

Other grounds that have been specified include: procurement of the registration by fraud or misrepresentation; violation of the conditions subject to which the drug was registered; public interest; contraventions of the provisions of the legislation; and misleading or exaggerated advertising.

New drugs require continuous monitoring. In Brazil, under normal conditions of marketing or large-scale distribution, a new medicament must carry a cautionary notice on the label during the first five years of use. This must state that the product is a new medicament, that research has indicated that if it is properly used it should be efficacious and safe, and that should unforeseen adverse reactions occur, the physician concerned must be promptly notified.

Problems associated with registration

One of the arguments often advanced against registration is the delay in processing applications. In Mali, the National Commission on Market-

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1 Pharmacy and Poisons (Registration of Drugs) Rules, 1981.
2 Order No. 11 of 4 September 1981.
ing Licences is legally bound to finalize its view on an application within four months. The time-limit is suspended if the manufacturer is requested by the Commission to supply additional information or to carry out additional tests. If the Commission is considering rejection of an application, the applicant must be notified so that within a period of one month he may make further representations. Such representations, if any, must be considered by the Commission when it transmits its views to the Minister. The Minister is required to substantiate any decision to reject an application. If countries issue administrative guidelines regarding the requirements of registration and the procedures to be followed and if manufacturers submit complete and comprehensive documentation, the delay in processing applications should be minimized.

An argument frequently advanced against regulatory measures is that they affect the rate of introduction of new drugs. Attempts have been made to use statistical data to demonstrate how regulatory stringency in the USA, for instance, has resulted in a decline in drug innovation. However, more recent studies have thrown doubt on these findings.

The cost of drug innovation has increased over the years and this cost factor looms large in the industry decision-making process. The development of a new chemical entity in 1983 was estimated by the industry to cost over US$ 50 million and to involve a time span of between 8 and 10 years.

Owing to the lack of resources for carrying out clinical tests (see Annex 4) and evaluating applications for registration, some countries tend to be guided by registration decisions made in the country where the drug is manufactured or in countries where the drug is used. However, there are disadvantages to this. For instance, a drug deemed unsuitable for distribution and use in one country may nevertheless make substantial contributions to the health needs of another country. "The relative safety and efficacy of a drug or medical device is a composite judgement which must be made by each country based upon many factors, such as the status of the health care system in that country, patients' compliance with dosage regimens, alternative therapies that may be available, and other specific characteristics of its population." In this connection, the WHO certification scheme on the quality of pharmaceutical products moving in international commerce (see Annex 3) provides a valuable alternative mechanism, as discussed on p.56.

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1 Interministerial Order No. 2135 MPS-AS.CAB of 27 July 1977.
Development of the registration scheme

In developing a registration system, a step-by-step approach has to be followed. ¹,²

An inventory of all the available drugs is a prerequisite for establishment of a registration system. Unless sufficient data are available from the existing import system, the inventory has to be prepared by requiring manufacturers, importers, and distributors to notify the drugs that they handle. This process is commonly referred to as the "notification procedure". The required information and data should be furnished on a prescribed form on or before a prescribed date. Adequate publicity regarding the requirement might make for a better and quicker response. If the notification procedure is accompanied by a threat of sanctions, such as an automatic ban on drugs in respect of which no notification has been made, the preparation of the inventory will be greatly facilitated. During the notification period and thereafter the introduction of new drugs must be made subject to prior evaluation and registration. In other words, the introduction of new drugs should be specifically authorized from the commencement of the notification procedure.

Once the notification phase is over, two alternative courses of action are available: (a) to begin the process of evaluating each of the inventoried drugs with a view to granting registration, or (b) to pick out first the drugs that need to be eliminated from the market and ban their use from a date to be specified. In either case, until a decision is communicated, all the available drugs should be allowed to remain on the market. Appropriate criteria need to be established for evaluation purposes. If a national formulary is prepared, drugs that are not listed can be gradually withdrawn from the market.

The establishment of a registration system is normally associated with a variety of problems. Shortage of manpower and technical resources for evaluation, administrative delays, non-cooperation of specialists, and the influence of vested interests are some of the well known contributory factors. The exchange of information between countries on the registration or non-registration of drugs can facilitate the procedures.¹

WHO certification scheme

Many developing countries are still in the process of evolving national capabilities to evaluate the quality, safety, and efficacy of drugs. In 1975, the 28th World Health Assembly adopted a certification scheme on the quality of pharmaceutical products moving in international commerce (see Annex 3). The objective of this certification scheme has been des-

ASSURANCE OF DRUG QUALITY, SAFETY, AND EFFICACY

scribed as being to provide “a simple administrative mechanism whereby importing countries can:

(1) obtain assurance that a given product has been authorized to be placed on the market in the exporting country, and if applicable, obtain information on the reasons for a product not being authorized to be placed on the market in the country of export;

(2) obtain assurance that the manufacturing plant in which the product is produced (a) is subject to inspections at suitable intervals, and (b) conforms to requirements for good practices in the manufacture and quality control of drugs, as recommended by the World Health Organization; and

(3) exchange information on the implementation of inspection and controls exercised by the authorities in the exporting country. In the case of serious quality defects in the importing or exporting country, such information and requests for inquiries may also be exchanged”.

The scheme offers a good alternative mechanism for countries that lack the capacity to carry out an independent evaluation of imported drugs. The text of the scheme is reproduced in Annex 3. It provides that a certificate may be requested whenever a product covered by the scheme has been placed on order. If a drug is not registered in the country of export, the reason for this lack of registration can be requested, e.g., the drug may be intended for treatment of a tropical disease. If the certified product, on importation, is found to be of inferior quality, the responsible authority of the importing country can be asked to initiate inquiries. At the present time some 108 Member States of WHO participate in this scheme. WHO is now formulating guidelines intended to improve its operation. Appropriate provision for the application of the scheme can be made in the regulations or in the licence issued for importation. In addition, bilateral trade agreements relating to pharmaceutical products can make provision for compliance with the scheme.

Dissemination of information

Since the early 1960s, the international health community has been increasingly concerned with the hazards of certain drugs. In 1963, the Sixteenth World Health Assembly stressed that international cooperation is essential for the achievement of the best possible protection against the hazards to man arising out of the use of drugs, and that action was needed to ensure the rapid dissemination of information on adverse drug reactions. Member States were requested to communicate immediately to WHO:

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1 Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Unpublished WHO document, Pharm/82.4.Rev.1.

2 Resolution WHA 16.36.
(a) any decision to prohibit or limit the availability of a drug already in use;
(b) any decision to refuse the approval of a new drug; and
(c) any approval for general use of a new drug when accompanied by restrictive provisions.

In the event of such a decision being taken as a result of serious adverse reactions, the reasons for the decision were also to be included, as far as possible, in the communication. The Director-General was requested to transmit this information immediately to Member States. Besides providing for a system of information to be channelled through WHO, the Assembly invited Member States to arrange for the systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use. The World Health Assembly has, from time to time, given its attention to the need to intensify communication strategies to facilitate the availability of safe drugs. In 1973, for instance, it reiterated its demand that all drugs made available to consumers should comply with adequate standards of quality, safety, and efficacy and stated that WHO has a major role to play in the collection and dissemination of information on drugs.1

In response to these concerns of the international health community, WHO has, over a period of years, developed several activities designed to facilitate the collection, analysis, and dissemination of information and data on the toxic effects of drugs. Some of these activities are:

(a) channelling of information to Member States, through a monthly communication, regarding decisions of national regulatory agencies with regard to restrictions on the availability and applications of drugs already in use;
(b) participation in a system, involving 27 national collaborating centres, for the monitoring of adverse reactions to drugs and the exchange and evaluation of information and data; and
(c) publication of Drug information, a bulletin dealing with general policy issues and also containing: short reviews of relevant literature on individual drugs that have been withdrawn or restricted in use by certain Member States; lists of new chemical entities registered recently in Member States participating in the international information system; and national regulatory decisions withdrawing or restricting the use of specific drugs, on grounds of safety or efficacy.

In addition to the above activities, the Organization periodically convenes expert committees to make recommendations on the selection and use of essential drugs. Also the two international drug control treaties, the Single Convention on Narcotic Drugs, 1961, as amended by the Protocol of 1972, and the Convention on Psychotropic Substances, 1971, have assigned to WHO the responsibility for evaluating psychoactive drugs in

1 Resolution WHA 26.31.
relation to a variety of risk/benefit factors, such as their therapeutic usefulness, their dependence-producing propensities, and the public health and social problems generated by them. The Organization collects information and data from Member States for the purpose of carrying out the evaluation. The decision of the Director-General with regard to the regulation of certain psychoactive drugs under the various schedules to the treaties is communicated to the Secretary-General of the United Nations and through him to all the countries to enable a final decision thereon to be made by the United Nations Commission on Narcotic Drugs.

It is of the utmost importance that the World Health Organization should be furnished with relevant information regarding drugs. Through appropriate legal or administrative arrangements, national regulatory authorities should be required to furnish such information to the Organization with the least possible delay. At the national level, legislation can be enacted making it obligatory for medical practitioners and related health professionals, including medical and scientific research workers, to notify the national regulatory authorities regarding toxic drugs or adverse reactions so that the authorities concerned may take appropriate measures for monitoring such drugs and any further action deemed necessary.

Since 1980, international conferences of drug registration authorities have been held biennially. An important item on the agenda at each conference has been the question of developing a communication network for information collection and dissemination.\(^1\)

**Quality Assessment and Assurance**

Drug quality assessment and assurance are of great importance and appropriate procedures have to be established for these purposes. The twenty-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations\(^2\) contains a document outlining the

\(^1\) It is of interest that the Third International Conference of Drug Registration Authorities, held in Stockholm in June 1984, noted that if pharmaceuticals are included in lists compiled in accordance with the various resolutions of the General Assembly of the United Nations regarding products banned, withdrawn, restricted or not approved, the listing should be presented in a way that provides an overview of the general or worldwide status of the listed pharmaceutical products. It was pointed out that regulatory decisions restricting the use of pharmaceuticals can be taken for a number of reasons, some of which may be specific to a country or region, and that it is essential to know the basis of such decisions. Furthermore, any information that is transmitted must contain the monograph or data sheets for the product and such other information as would be useful in enabling national regulatory agencies to make an informed decision about the product. A memorandum of understanding has recently been concluded between WHO and the UN Secretariat, which accords to WHO the responsibility for collecting, processing and screening information relating to pharmaceutical products in the light of the agreed criteria, as well as for clarifying, with the governments concerned, information that is considered to be insufficient and/or of questionable relevance.

elements of a drug quality assessment and assurance system, covering manufacture, pre-marketing and marketing. The main points of this document are summarized in Annex 5.

The remainder of this chapter deals with several specific issues that are of importance in drafting and implementing drug legislation.

Pharmacopoeias

Pharmacopoeias provide “standards that are publicly available and that allow independent evaluations of drug quality to be made at any stage after the drugs have left the manufacturer’s care and prior to their utilization.”¹ The applicable pharmacopoeia or pharmacopoeias must be specified in the legislation. The *International Pharmacopoeia* published by WHO “constitutes a collection of recommended methods and specifications that are not intended to have a legal status as such in any country, unless expressly introduced for that purpose by appropriate legislation, but are offered to serve as references so that national requirements can be established on a similar basis in any country”.² Some countries, such as Sri Lanka³ and Chile,⁴ have specifically provided that *The International Pharmacopoeia* should be used in the country. It is of interest to note that Chile also has a national pharmacopoeia.

Quality control laboratories

Quality control laboratories are necessary for conducting routine tests on samples and performing other investigations. Such tests and investigations must be carried out expeditiously to enable enforcement personnel to take appropriate action, if the need arises. For tests involving complicated or sophisticated equipment or facilities not available in a country, the assistance of more advanced laboratories in other countries should be sought. While collaborative arrangements can be made administratively, it is also possible to accord legal sanction to such arrangements. For instance, a decree enacted in 1969 in the Congo requires the National Public Health Laboratory in Brazzaville to maintain close scientific and technical relations with the Pasteur Institute in Paris.⁵

In its twenty-ninth report, the WHO Expert Committee on Specifications for Pharmaceutical Preparations⁶ emphasized that: “every country, regardless of its stage of development, should consider the need

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³ Act No. 27 of 1980.
⁴ Decree No. 435 of 1981.
⁵ Decree No. 118 of 5 February 1969.
for investment in an independent national drug quality control laboratory". The Committee called for special status to be accorded by statute to analytical reports issued by such laboratories. It noted that "even the existence of a single small laboratory, when it is concerned with priority issues and perceptively managed, can offer a deterrent against unscrupulous or negligent manufacturing and trading practices. It is also evident that standards of local manufacturers will tend to rise whenever the possibility of an independent assessment of the quality of their products exists".

Drugs inspectors

Drug inspectors, examination of samples, inspection of pharmacies and retail outlets, etc. are matters that have to be provided for in the substantive legislation or at least in regulations. The power of inspection must be granted by the principal legislative instrument. According to Di Lorenzo, the primary objective of a drug plant inspection is "to uncover weaknesses and deficiencies in manufacturing procedures and operations . . . [as well as] . . . actual or potential errors in production and quality control procedures". Inspections of a drug plant may fall into one of the following categories:

1. routine, periodic inspections as required by the national drug control agency;
2. a follow-up inspection to ensure that recommendations made at a previous inspection have been implemented;
3. inspection of a new plant for licensing purposes;
4. inspection of changes in the firm's manufacturing operations and procedures or a major change in plant layout;
5. the follow-up on a drug that has been removed from the market because it did not meet established standards, laboratory assays had indicated that the potency was not as declared on the label, unanticipated toxic reactions had been reported from the drug, etc.;
6. an inspection to obtain scientific information on a specific drug or to obtain samples.

Inspection of premises that are licensed for the manufacture, storage, and sale of drugs must be done by drug inspectors, customs officials, etc., who are duly authorized. A drugs or medicines inspectorate can be established by legislation. Alternatively, legal provision can be made for the central regulatory agency or for the head of the health services to authorize designated persons to carry out inspections and to obtain samples. To facilitate testing, the law can provide for the services of officers of other agencies, such as the department of the government analyst, to be enlisted.

Drug inspection exercises must be related to measures designed to augment the quality of drugs. The cancellation of licences and permits, the withdrawal or recall of drugs from the market, and penal sanctions have to be specifically provided for in the legislation. In order to facilitate legal proceedings, the law can stipulate that the burden of proving or disproving certain matters rests on the manufacturer or distributor against whom legal proceedings have been initiated.

It has been said repeatedly that the drug inspector serves as the eyes and ears of the drug control authorities. Perhaps the drug inspector must also serve as the eyes and ears of the manufacturer, the distributor, the doctor and last, but not least, the consumer. Drug inspection need not be viewed with suspicion; a drug inspector need not be treated as a detective. A better term than “drug inspector” might be “drug activities coordinator” which would be more appropriate in the context of the wider functional role envisaged.

Sanctions for contravention

A drug law must lay down appropriate sanctions for contraventions of the provisions in the principal statutory instrument and in the subsidiary legislation. Even though, for hazardous products such as drugs, it is desirable that priority be accorded to vigorous law enforcement efforts followed by the institution of legal proceedings, it needs to be borne in mind that “education and persuasion are much more effective in protecting the public than the initiation of legal action, which may result in a long and expensive court case”. While certain legal systems permit specially authorized enforcement officials to institute legal proceedings and to conduct prosecutions, yet in matters involving complicated issues of fact or law, it is advisable to seek the assistance of a law officer, such as the attorney-general. Courts need to be vested with the power to suspend or cancel a permit or licence in respect of serious offences. The law must provide that the manufacturer or distributor can be charged if the court is satisfied during the course of the trial that such manufacturer or distributor carries responsibility for the offence.

Legal measures and sanctions have to be augmented by other appropriate measures covering educational and marketing aspects. Educational and technical programmes for scientists, technical personnel, pharmacists and distributors of drugs must underline the importance of quality. Good marketing ethics must be inculcated to ensure that only quality products are sold.

Enforcement and monitoring activities must be carried out regularly, with appropriate arrangements for feedback and interaction. Enforcement and monitoring systems must be periodically reviewed. The capacity for enforcement is a relevant consideration in deciding on the type of legal structure best suited to the needs of the country.

CHAPTER 11

Legal framework relating to the sale and distribution of pharmaceuticals

The mechanics and strategies of distributing and marketing drugs constitute an integral component of any national drug policy. Drugs must reach the consumers who need them and do so at the right time. A policy would leave much to be desired if its implementation did not lead to the achievement of this objective. In many developing countries, the lack of appropriate channels of distribution may mean that any drug policy will not be immediately relevant to the rural population.

A drug law cannot by itself ensure that drugs reach those in need of them, but it has the potential to facilitate the establishment of efficient channels of distribution.

Drugs constitute a special kind of consumer commodity, which must not be indiscriminately distributed. In Togo, it was recently found necessary to enact legislation1 to prohibit distribution of drugs on public highways, at fairs, and in markets. This prohibition applies even if drugs are given free and the person giving them is a qualified pharmacist. A drug law must stipulate who is entitled to distribute drugs, how and where they should be distributed, the type of safeguards and controls subject to which distribution can take place, who is entitled to receive drugs, the maximum prices at which the drugs may be sold, etc. For this purpose, the law must assign responsibility, authorize functions to be performed, and spell out the rights and duties of prescribers, distributors, patients, etc.

The control over the distribution and sale of drugs can take various forms:

1. The places where drugs are stored prior to distribution or for purposes of distribution can be regulated through a licensing system. Such a system, if properly implemented, ensures that drugs are properly stored and facilitates the work of drug inspectors. Stipulations regarding labelling, repacking, etc., can be imposed by way of regulations or as conditions of issue of the licence.

2. The persons authorized to distribute drugs can be regulated by law. There can be different licences or control systems in respect of the

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1 Decree No. 81-61 of 30 March 1981.
different distributors, such as pharmacists, wholesale and retail drug dealers, etc.

3. The manner of distribution can be regulated. By and large, the restrictions relating to the types of drug available for distribution recognize two categories — "prescription drugs" and "non-prescription drugs" (or "over-the-counter drugs"). In addition, the law can stipulate that certain outlets distribute only essential drugs. The specification of various categories of drug can be done by way of a schedule to the main statute or to the regulations. Many legal systems permit a responsible authority, such as the minister of health or the director of health services, to add to or delete from the schedule any item at any time. Such a method provides flexibility in drug regulation.

4. Prescribers can be required to use generic names when prescribing drugs. Medical and paramedical personnel in certain institutions can be required to prescribe essential drugs in the first instance, unless there are therapeutic reasons for prescribing other drugs.

5. The law can regulate the categories of persons who are entitled to obtain drugs. For instance, in some countries the sale of oral contraceptives has been restricted to persons over a particular age. There are certain drugs that should be made available only to a person who has a prescription.

Many countries have two types of licensing system. For instance, in Sri Lanka\(^1\) no person is allowed to sell or distribute or offer for sale any drug without a licence issued by the Cosmetics, Devices and Drugs Authority. Furthermore, no person may prepare, store or sell any drug in any premises unless the premises have been licensed by the Authority. For purposes of the licensing system, the expression "sell" means "to sell for cash or on credit or by way of exchange whether by way of wholesale or retail". Licences can specify the types of drug that can be sold only by certain categories of persons, such as drug retailers.

In many countries, government or state-sponsored hospitals or private pharmacies are the main outlets for the distribution of drugs. Quality assurance, sanitary and hygienic standards, etc. should apply irrespective of whether the outlet is part of the public sector or not, and drug inspectors should be required to monitor both public and private sector outlets.

Enforcement personnel, such as drug inspectors, must apprise pharmacists of the need to maintain their premises in a condition suitable for the storage of drugs. Furthermore, pharmacists and drug retailers ought to be kept informed of all important policy and legal changes. Programmes for their professional betterment will enable them to keep abreast of the more important developments in the field of pharmacology. Pharmacists perform an important function and they should be equipped to discharge their duties and responsibilities in a proper fashion. For instance, in Algeria the law\(^2\) requires all pharmacists in charge of pharmacies or estab-

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\(^1\) Act No. 27 of 1980.

\(^2\) Decree No. 76-139 of 12 October 1976.
lishments for the preparation, sale, or wholesale distribution of medications to have in their possession at least one copy of the pharmacopoeia and its supplements. It is useful to grant import duty concessions in respect of equipment that pharmacists require for their day-to-day activities.

Inasmuch as one of the priority areas for drug policy-makers is the identification of better mechanisms for drug distribution, it is useful to look at some of the legislative provisions relating to the registration of medical practitioners, their right to dispense drugs, etc., even though such provisions may be found not in the law on pharmaceuticals but in some other law such as, for instance, a medical practitioners act.

Some countries do not allow medical practitioners to practise medicine and pharmacy simultaneously. Some codes of professional conduct, too, regard such joint practice as unacceptable. However, to augment the delivery of health care services, developing countries have considered alternative models. For instance, in Rwanda, private physicians are authorized to keep and supply pharmaceutical products if there is no pharmacy open to the public within a radius of 10 km.1

One of the reasons why developing countries have found it difficult to extend national health care systems to cover a significant segment of the population is the shortage of qualified medical practitioners and paramedical personnel. Even though many countries have expanded and intensified medical training programmes, it has not been possible to stem the tide of migration to more developed countries, which offer higher wages and better conditions of living and working. Faced with this problem, some countries have devised schemes to combat this “brain drain”. In Sri Lanka, for instance, a Compulsory Public Service Act2 was enacted in 1961 requiring newly qualified medical practitioners to work in Sri Lanka for a period of five years. Another problem is that medical practitioners tend to be concentrated in urban areas, where they may expect better living conditions and prospects of higher income. In the absence of any rapid development of the infrastructure, rural areas have very little to offer to reverse the flow and attract qualified medical personnel. It is of interest to note that in 1956 a decree3 was enacted in Colombia prohibiting persons who have graduated from recognized medical schools from practising medicine in Colombia unless they have served for at least 12 months in the rural health service. A similar decree was enacted in 1962 in Lebanon requiring newly qualified physicians who have not practised before in Lebanon to work in rural areas for at least two years.4

In relation to the registration of pharmacists and the location of pharmacies it has to be noted that throughout the developing world there is an acute shortage both of trained manpower and of distribution outlets. The problem is particularly acute in Africa and the view has been expressed that “the greatest need of African countries in the area of phar-

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1 Ministerial Order No. 001/1.2.12/81 of 1 September 1981.
2 Act No. 70 of 1961.
3 Decree No. 3130 of 20 December 1956.
4 Decree No. 10823 of 9 October 1962.
maceutical development and drug control is the training of the necessary personnel". In Burkina Faso, for instance, one pharmacy serves the needs of nearly half a million people. Legal provisions regulating the location of pharmacies make possible a more equitable distribution, though this is a question that has so far received very little attention. In Senegal, a decree was enacted in 1981 prescribing criteria for the establishment of pharmaceutical dispensaries. While each regional or departmental administrative centre and each commune must have a pharmaceutical dispensary irrespective of the population the dispensary would serve, no dispensary can be established in the Cap Vert region (the region surrounding Dakar, the capital) unless the number of inhabitants to be served is at least 15,000. The minimum population target in respect of other regions is 30,000 inhabitants. These criteria are to be revised every five years. In Benin, the National Pharmaceutical Office is required by law to establish a supply point (dépôt) in each provincial capital. The Pharmaceutical Supplies Centre, the Health Service of the People’s Armed Forces, the independent hospital centres, private pharmacies and local authorities must obtain their requirements from the dépôt. Other users of products marketed by the National Pharmaceutical Office have to obtain them through private pharmacies and local authority sales outlets. In Algeria, the Algerian Central Pharmacy is required by law to establish State pharmaceutical agencies in all communes in order to ensure that patients have easy access to basic pharmaceutical products.

Some countries have authorized non-pharmacy retail outlets in localities in which there are no pharmacies or druggists’ shops. For instance, in 1955 Colombian authorities authorized shopkeepers to sell pharmaceutical products that do not require prescription, provided there is no pharmacy or druggists’ shop in the locality. Shopkeepers have to be licensed for the purpose. In the event of a pharmacy being established in the locality, all stocks have to be disposed of within 90 days.

The purchase of a drug by the consumer does not end the responsibility of the manufacturer, the regulatory authority, the prescriber, or the dispenser. For instance, there can be a legal requirement that if an importer, manufacturer, doctor, pharmacist, or distributor has reason to believe that any severe adverse reactions or substantial untoward effects have arisen from the use of a drug, whether in the country or elsewhere, the person should take steps to inform the health authorities concerned. Appropriate preventive methods should be taken in consultation with the authorities. Post-marketing surveillance, however, is something that is relatively new to most countries. It was noted in Chapter 10 that the WHO certification scheme on the quality of pharmaceutical products moving in

2 Decree No. 81-244 of 13 March 1981.
3 Ordinance No. 78-29 of 14 August 1979.
4 Decree No. 77-6 of 23 January 1977.
5 Resolution No. 221J of 11 February 1955.
international commerce requires the importing country and the exporting country to notify each other of serious defects in pharmaceutical products.

Specific measures for the protection of consumers that go beyond the traditional areas of regulation have not yet found their way into most national laws. A few countries do have innovative provisions that are indicative of the extent to which the interests of the consumer can be protected. In Brazil, the law¹ requires all reports on accidents and adverse reactions caused by medicaments to be submitted to the competent health authority. The Nepali Drugs Act² provides for the payment of compensation to drug victims. Issues of causation and liability loom large in attempts to define the circumstances in which a manufacturer or a doctor, for instance, is liable in respect of an injury sustained by a consumer. Some countries have adopted various measures, such as the introduction of a no-fault compensation system and the extension of the doctrine of “strict liability”, to protect and promote the interests of the consumer.

¹ Law No. 6360 of 23 September 1976.
² Act No. 21 of 2035 (1978).
Control of information on pharmaceuticals, including labelling and advertising

While requirements relating to information on pharmaceuticals and to labelling and advertising are generally included in the substantive statute or regulations dealing with pharmaceuticals, a few countries have enacted special statutes. For instance, in 1954, India enacted a separate substantive law dealing with advertisements: the Drugs and Magic Remedies (Objectionable Advertisements) Act prohibits not only the internal publication of advertisements for certain specified illnesses and diseases but also the importation to or exportation from India of certain kinds of advertisements. In Malaysia, advertisements are screened by a Medicine Advertisements Board, in accordance with the Medicines (Advertisement and Sale) Act, 1956.

For effective control, the definitions of “labelling”, “advertising”, and “information” need to be broad. For instance, the definition of “advertisement” in the Bangladeshi legislation includes any announcement made orally and any notice displayed on public transport. Even labels are covered by this definition. To take another example, the regulatory provisions in Singapore extend to door-to-door sales promotion.

Different countries have devised different kinds of control strategies. Some countries have specific requirements regarding labelling and advertising, such as prior approval or mandatory inclusion of certain details. Other countries have negative stipulations, such as that an advertisement should not contain any false statements.

The regulation of labelling is easier than that of advertising because the latter is a multidimensional method of communication. There can be a legal requirement regarding the minimum information that should appear on the label of a product, together with appropriate instructions and warnings. Labels, package inserts, and advertisements can be scrutinized with a view to approving them, with or without modifications. In the case of advertisements, different requirements would be needed for different kinds of advertisement. Drug advertisements cater to different target

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1 Act No. XXI of 1954.
2 Ordinance No. VIII of 1982.
groups — doctors, patients, retailers, etc. — and deal with different categories of drug — prescription drugs, non-prescription drugs, etc. Different regulatory provisions can be formulated to regulate the different situations in which a manufacturer or distributor might advertise. In fact, national laws represent such a wide spectrum of regulatory patterns that all that is possible in the present text is to set out the position in a few countries.

In Ecuador,\(^1\) for example, there are two different sets of provisions dealing respectively with labels and advertisements. Labels must be submitted for approval within three months of the registration of the product, and must indicate: the name of the product; the pharmaceutical form; the net contents of the package; the qualitative and quantitative formula; active principles and other components; the routes of administration; the batch number; any contraindications or warnings; whether for paediatric use; the storage temperature (if appropriate); whether a prescription is required; the name and address of the manufacturer; the name of the pharmacist responsible for preparation (if appropriate); the date of preparation and expiry date; and the registration number. If the size of the packaging is small, only the name of the product, the name of the manufacturer, the batch number, the concentration of the active principle, the expiry date, and warnings, if any, need appear on the label. The General Directorate of Health can require warnings, such as “to be sold only on medical prescription” or “may be habit-forming”, to appear on the label. In addition to other warnings, the label of every over-the-counter medicament must state that if the symptoms persist, a physician should be consulted. The labels of medicaments intended for promotional purposes must state that they are samples not intended for sale. No drawings or figures suggestive of the therapeutic value of the product or inciting the public to use it are allowed to be printed on any label, packaging, or package insert. Names that suggest improper uses or the presence of active principles that are in fact not present or that exaggerate the therapeutic properties of the product are not permitted.

The Ecuadorian Law requires the text of every advertisement of any medicament intended for dissemination by any means to be licensed by the General Directorate of Health. The advertising of medicaments by word of mouth on the public thoroughfare is absolutely prohibited. No public advertisements are permitted in respect of medicaments that require a prescription; non-prescription drugs may be advertised, provided that a warning is included that a physician should be consulted if the symptoms persist. Section 52 of the law specifies that “medical advertising shall conform to scientific truth and the provisions of health legislation, indicating both the favourable and unfavourable characteristics of the product”.

Every advertisement must indicate the dosage and indications, as well as warning texts, precautions for use, contraindications, and side-effects. It is not permitted to include any medical literature in a package.

\(^1\) Order No. 8022 of 20 July 1977.
The Ecuadorian approach can be compared with that of Sri Lanka. Under the Cosmetics, Devices and Drugs Act\(^1\) there is no provision for prior screening of labels or advertisements. The control mechanisms are based on negative stipulations, contravention of which will lead to penal consequences. The terms "advertisements" and "labels" are defined in the Act. The former term includes "any representation by any means whatsoever for the purpose of promotion, directly or indirectly, the manufacture, sale or disposal of any drug" (section 40). Any tag, brand, mark, pictorial or other descriptive matter, written, printed, stencilled, marked, embossed, or impressed on, or attached to a container of a drug is included within the definition of "label". Under the Act, it is prohibited for any person to label or advertise any drug in a manner that is false, misleading, deceptive or likely to create an erroneous impression regarding its character, value, potency, quality, composition, merit, or safety. For purposes of penal liability, this prohibition is deemed to apply to any drug that is not labelled as required by regulations made under the Act. Where a standard has been prescribed for a drug or a standard for that drug is contained in the International Pharmacopoeia, the British Pharmacopoeia, the United States Pharmacopeia, the British Pharmaceutical Codex, the British Veterinary Codex, the Pharmacopoeia of Japan, or the European Pharmacopoeia, no person is entitled to label or advertise any drug that does not conform to the standard in such a manner that it might be mistaken for the drug to which the standard applies. If a standard has not been prescribed for a drug, either in the Act or in one of the publications listed above, no person is entitled to sell, offer for sale, or distribute that drug (a) unless it is in conformity with the standard set out in the label accompanying the drug; or (b) in such a manner that it might be mistaken for a drug for which a standard has been prescribed. The Act does not permit any person to distribute or cause to be distributed any drug as a sample, but there is provision for conditions to be laid down for the distribution of a drug to medical practitioners, dentists, or veterinary surgeons. In addition to the above requirements and stipulations, the Act contains two other restrictions that are related to certain diseases, disorders, or abnormal physical states set out in two schedules to the Act. The first restriction places an absolute prohibition on advertising any drug to the public in respect of diseases or disorders included in the first schedule. The other prohibition is on importing, selling, offering for sale, or distributing any drug that is labelled, or advertised to the public, as a treatment for the diseases or disorders set out in the second schedule.

In countries with prior screening requirements, different authorities have been designated to carry out the screening. For instance, in Malta\(^2\) the law requires that all advertisements should be subject to the prior authorization of the Superintendent of Public Health, who has to act on the advice of the Council of Health. In Malaysia\(^3\) there is a Medicine

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\(^1\) Act No. 27 of 1980.

\(^2\) Control of Advertising of Medicinal Regulations, L.N. 85 of 1981.

\(^3\) Medicine Advertisement Board Regulations, 1976.
Advertisements Board, headed by the Director-General of the Ministry of Health. The Director of Pharmaceutical Services, a physician, a pharmacologist, a pharmacist and an officer from the Ministry of Information are other members of this Board. At the 1981 WHO Consultation on Basic Elements of Drug Legislation and Regulatory Control for Developing Countries¹ it was recommended that countries desirous of screening information and advertising materials should have a multidisciplinary committee consisting of representatives from:

- the drug control agency;
- the pharmaceutical manufacturing industry;
- the pharmaceutical profession;
- the medical profession;
- the news media; and
- the advertising agency.

Labelling and advertising material for the public should be in a comprehensible language. This is important, especially in relation to information on recommended dosage, possible contraindications, and side-effects. In Brazil, the law² requires that contraindications, precautions and side-effects must be:

(a) in a larger type-face than that used for the remaining particulars; and
(b) in easily understandable language.

Some countries do not permit the use of certain expressions in labelling and advertising texts. For instance, a decree enacted in El Salvador in 1959³ prohibits the use of any expression or term exaggerating the virtues of a product or a pharmaceutical speciality, such as “wonder drug”; “magic”; “the best”; or “the most powerful”.

Labelling requirements vary from country to country. Some countries have specific requirements for specific drugs or groups of drugs. General prohibitions, too, vary from country to country. In Guyana, for instance, there is a requirement⁴ that every label or prepackaged drug must bear the cautionary phrase “Keep out of reach of children”, which should be prominently displayed and readily discernible. Ecuador requires the statement “if the symptoms persist, consult your physician” to appear on every label in respect of over-the-counter medicaments.⁵ The identification of the minimum information required is difficult since “the total mass of information that exists about any individual drug is overwhelming,

² Law No. 6360 of 23 September 1976.
³ Decree No. 96 of 19 November 1959.
⁴ Food and Drug Regulations No. 10 of 1977.
⁵ Order No. 8022 of 20 July 1977.
even when the drug is relatively new". It is difficult to make any quantitative assessments of the information required by the categories of people who need to use or have access to such information. It has been suggested that, in terms of typewritten pages, the information required by the various categories would probably be of the following orders of magnitude:

(a) The pharmaceutical industry — 4000 pages
(b) The regulatory agency — 2000 pages
(c) Academic investigators — 500 pages
(d) Prescribers — 20 pages
(e) Patients — 2 pages.

Reducing 4000 pages of information to a meaningful summary of two pages for the patient’s use will be possible only if the industry has a proper perception of the needs of patients and is willing to make a full disclosure of the hazards and contraindications about which patients need to be warned. The regulatory agency and medical scientists need to scrutinize this information, not only with regard to accuracy but also in relation to comprehensiveness from the patients’ point of view. The prescriber should bear in mind that the amount of information that patients need to have is variable and must exercise his or her own judgement as to whether it is necessary to furnish additional information or instructions when a particular drug is prescribed for a particular patient. The criteria of “necessary information” will, of course, always remain debatable, though “minimum information sheets” in respect of different drugs help the prescriber and the patient to a certain extent.

In 1968, the Twenty-first World Health Assembly urged Member States to enforce controls on advertisements. The text of the resolution deals with the ethical and scientific criteria for pharmaceutical advertising and covers advertising to the medical and related professions as well as to the public.

It has often been said that there must be a fair balance in the presentation of information regarding the merits and demerits of drugs. From the perspective of consumer protection, it is important that the consumer

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3 Resolution WHA 21.41 of 23 May 1968.
should be alerted to all side-effects, contraindications, warnings, hazards, and precautions. It has been observed\(^1\) that a fair balance can be considered to be lacking if:

\(\text{(a)}\) information is included in an advertisement that has not been approved for inclusion in the promotional material at the time of registration;

\(\text{(b)}\) advantages are claimed for the drug without simultaneous disclosure of disadvantages;

\(\text{(c)}\) obsolete information is used;

\(\text{(d)}\) claims are exaggerated;

\(\text{(e)}\) animal or laboratory data are cited as clinical experience;

\(\text{(f)}\) a statement by a recognized authority is quoted without also citing any unfavourable opinions of that authority;

\(\text{(g)}\) statements are used out of context;

\(\text{(h)}\) statistics are used in a misleading way; and

\(\text{(i)}\) a headline or pictorial presentation is misleading.

In the case of imported drugs, drug inspectors should ensure that the labels conform to local requirements. Products with labels not conforming to such requirements should not be allowed to be displayed or sold. The law can provide for delicensing, relabelling, export, or forfeiture of products with inappropriate labels. For instance, in Kenya, an imported drug can be relabelled under the supervision of an authorized officer so that it conforms to the local requirements. If such relabelling is not satisfactorily carried out within three months, the drug must be exported to a destination disclosed to the authorized officer.\(^2\) There is a similar provision in Guyana.\(^3\) If the goods are not exported within three months, they become forfeit to the State. The Minister is empowered to give directions as to how the drugs are to be disposed of.

During the last few years the need for accurate and full disclosure in respect of labelling and advertising has been underlined by several writers\(^4\) who have made comparisons between practices in different parts of the world.\(^5\)

\(^1\) *Guidelines for the development of a national drug control program.* Unpublished document (no date) of the Pan American Health Organization, Washington, DC, pp. 79–80.

\(^2\) *Food, Drugs and Chemical Substances (General) Regulations, 1978.*

\(^3\) Regulation No. 10 of 1977.


The industry has not been unresponsive to the calls for a more responsible and judicious approach in promotional activities. The International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) Code of Pharmaceutical Marketing Practices, for instance, spells out the commitment of the industry in respect of such activities.

The regulation of the activities of drug sales promotion personnel is an area that is of increasing concern to developing countries. A few countries have made legislative provisions dealing with such personnel in particular and the use of drug samples in general.

The Pharmaceuticals and Poisons Act of 1978 of the United Republic of Tanzania empowered the Minister, after consultation with the Pharmacy Board, to make orders regulating “the recruitment and the medical activities of medical representatives.” Such orders can provide for licensing, registration, and payment of fees on application. The Minister can require that persons who are recruited as medical representatives must have attained a prescribed standard of academic education and a measure of practical knowledge of pharmacy. Orders have been made regulating the activities of medical representatives who distribute free samples of pharmaceuticals or pharmaceutical products containing certain specified poisons. A medical representative can have samples of such products in his possession or under his control and supply them free to persons who satisfy him that they may lawfully possess the specified “poisons”, provided that within 24 hours after supplying such samples the following particulars are entered in a book maintained for that purpose:

(a) the date on which any “poison” is supplied;
(b) the name and quantity of the “poison” supplied; and
(c) the name and address of the person to whom the “poison” is supplied.

The Tanzanian legislation breaks new ground not only by specifying the qualifications and providing for the registration of those who are eligible to be medical representatives, but also by monitoring the issue of free samples. As far as the latter are concerned, the present regulations cover only pharmaceuticals or pharmaceutical products containing specified “poisons”. But the legislative formula is nevertheless capable of being extended on similar lines.

Regulatory measures in other countries, too, are suggestive of possible approaches. For instance, in Chad only products that are licensed can be given as medical samples to physicians, pharmacists, midwives, dentists and veterinarians. Their resale to the public is prohibited. In Sri

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3 Pharmaceuticals and Poisons Act No. 9 of 1978, section 19.
4 Pharmaceuticals and Poisons Regulations of 31 December 1980.
5 Decree No. 87-66/PR of 18 April 1966.
Lanka,\(^1\) no person can distribute or cause to be distributed any drug as a sample. However, the legislation makes provision for the conditions under which samples can be supplied to medical practitioners, dentists, or veterinary surgeons to be prescribed. In Pakistan, samples can be given to physicians, dentists, pharmacists, veterinarians, or medical institutions only “in a reasonable quantity and in reduced packings marked with the words ‘Physician’s sample — not for sale’.”\(^2\) An important legislative provision in Pakistan imposes a ceiling, of 5% of the turnover, on the expenditure that can be incurred in connection with drug advertising, sampling, and other promotional activities.\(^3\)

In a sensitive and emotionally charged area such as drug information, labelling, advertising, and promotion there is a pressing need for compromises to be reached by all those who have an interest in the well-being and safety of the consumer. Legislative interventions in this area must seek to reconcile conflicting interests and evolve satisfactory formulae. Voluntary adherence to high ethical standards is as important as formulation and enforcement of sound legal controls.

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\(^1\) Cosmetics, Devices and Drugs Act No. 27 of 1980.
\(^2\) Drugs (Licensing, Registering and Advertising) Rules, 1976, Rule 32.
\(^3\) Drugs (Licensing, Registering and Advertising) Rules, 1976.
Some specific areas of regulation

This chapter deals very briefly with some areas of regulation that are of particular significance to developing countries. Legislative developments in these areas have not been universal nor are the national experiences sufficiently wide and varied to provide guidelines for regulatory models.

Generic Names and Generic Drugs

The conceptual issues relating to "generic names" and "generic drugs" have given rise to some degree of confusion.¹

A generic name — which is nonproprietary and usually contains a stem reflecting the pharmacological class to which the drug belongs — cannot become the exclusive property of any individual person or corporate body, as can brand or trade names. Generic drugs, or drugs marketed under their generic names, are usually cheaper than branded drugs.

Some countries have attempted to abolish the use of trade names, at least for products containing a single active ingredient. Some of the arguments against the use of brand names instead of generic names are:²

(a) the use of brand names involves unavoidable promotional expenditure, making drugs costlier;
(b) it is often difficult for domestic manufacturers to compete with subsidiaries of transnationals using established brand names; the growth of the domestic industry may therefore be hindered;
(c) the use of brand names allows some firms to sell drugs at high prices (much more than is justified by marketing expenses), even though technically these drugs may be only as effective as other products sold more cheaply under generic names; and

(d) allowing brand names encourages the flooding of the market with unnecessary combinations of drugs.

While in legislative terms the transition from brand names to generic names can be accomplished by a single stroke of the draftsman’s pen, there are operational problems that health administrators must be prepared to meet to ensure that the transition is smooth. The following passage describes two such problems based on the experience of a developing country that had attempted to bring about this transition through administrative measures:

“Reform of the marketing system requires tackling two distinct problems: first, ensuring that the cheaper generic products are of adequate quality and are biologically equivalent with the branded products of the TNCs [Transnational Corporations]; and second, ensuring that the change from brand to generic names is accepted by prescribers, who are provided information on the proper use of drugs by means other than private brand promotion.”

In considering whether a country is ready to ban the use of brand names, it is useful to bear in mind that even the use of generic drugs raises problems for society. The problems are both short-term and long-term:

“In the short-term, the growth of the generic market has encouraged the entry of many new companies into the market place. Society has no assurance that quality is being traded at the expense of price by smaller generic companies who do not have the funds to support an adequate quality control infrastructure or provide comprehensive product liability insurance. The second concern for society is long-term. A significant market conversion to low margin products from high margin patent lapsed specialities would weaken both the desire and the ability of the technology-intensive companies to continue their long-term commitment to investing in innovation. Weakening the ability of companies to perform the transformation from scientific discovery to usable product will ultimately reduce society’s access to future new products.”

Not all national experiments with the compulsory use of generic names have met with success. This is what two commentators have said about the 1972 Pakistani Drug (Generic Names) Act which banned brand names:

“The end result was the flooding of the market by a number of spurious drugs, many of which had problems of efficacy and safety. This eventually led to prescribers reverting back to branded products produced by reputable manufacturers, in fact strengthening the multi-nationals’ market penetration in many cases.”

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3 Act No. XXIV of 1972.

The Act was repealed after a few years.

A gradual transition, beginning with a limited category of essential drugs, accompanied by sufficient manpower for monitoring compliance with the new requirements is perhaps the only way to prevent a recurrence of the setback experienced by Pakistan.

One of the measures advocated to popularize the use of generic names and thereby ensure substantial financial savings, both to the economy of the country and to the consumer, is that pharmacists should be entitled to substitute a drug of a lower price for one that has been prescribed. The Barbados Drug Service Act of 1980 has given effect to this principle. Unless the person prescribing a drug specifically directs otherwise, the pharmacist dispensing the drug can supply an equivalent pharmaceutical product of lower cost than the one prescribed. The Act states further that no liability attaches to a pharmacist or a person prescribing a drug by reason only of the fact that the pharmacist has dispensed an equivalent pharmaceutical product.

Problems with Patents and Trade Marks

The regulation of patents and trade marks is not generally a matter that comes within the purview of health policy-makers and administrators. It is a matter for the authorities in charge of trade and industrial activities. However, the legislative provisions covering patents and trade marks have far-reaching implications for the use of generic names, the local manufacture of drugs, the import of drugs from cheaper or non-traditional sources, etc.

A manufacturer of drugs is entitled to apply for either a patent on processes or a patent on products. A patent on processes is of a limited nature, preventing only the use of the patented method. A product patent, on the other hand, prevents the entire range of activities involved in marketing the product — from manufacture to sale, importation, etc. Voluntary licensing agreements are normally granted on the payment of a fee, which may be in the form of royalties, to be paid periodically. The granting of patent rights to a manufacturer entails substantial financial implications for the country granting such rights. It also creates a monopoly situation in respect of importation or manufacture, or both. Developing countries have not been oblivious to the adverse cost-benefit implications of granting patent protection. Some 30 to 40 countries exclude pharmaceutical products from patent protection. A few countries have even excluded pharmaceutical processes from patent protection. Restriction of the duration of patent rights in respect of pharmaceutical products and processes is another modality that has been adopted. A system of granting compulsory licences ensures that protection is not abused.

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1 Act No. 58 of 1980.
Patent licensing agreements, even when granted, can have restrictive clauses and conditions that may not be in the best interests of developing countries. Several countries have imposed limitations relating to patent licensing arrangements. Among the abusive practices that have been regulated are: territorial restriction on exports; restriction on sources of supply of raw materials, spare parts, intermediate goods, capital goods, etc.; package licensing; excessive prices and royalty payments; and limitations on field of use.

According to recent estimates, more than 40% of the trade marks used throughout the world relate to pharmaceuticals and associated goods. For some 700 drugs there exist almost 20,000 names. The wide range of brand names is not a phenomenon confined to the developed countries. Markets in developing countries are known to have some 14,000 - 17,000 pharmaceutical brand names. The brand name system and the patent system are complementary in their effects on the drug industry: they both insulate the major drug companies from price competition. The advantage of the brand name system is that a brand name may be effective where a patent is not, e.g., for products that cannot be patented, or that are freely licensed, or for which the patent has expired.

Measures to regulate the patent and trade mark systems must be taken with long-term goals in mind and in collaboration with officials in trade and industrial development sectors. Programmes designed to effect the transfer of technology among developing countries need to be encouraged to complement such measures.

International Nonproprietary Names

The system of assigning international nonproprietary names to pharmaceutical substances has been in operation, under the aegis of the World Health Organization, since the early 1950s. A “nonproprietary name”, as the expression suggests, is a name that must remain in the public domain, free to be used by anyone, and cannot become the exclusive property of any individual person or corporate body; it is a generic name. An international nonproprietary name (commonly abbreviated as INN) is one that is valid worldwide, thus facilitating identification in any part of the world.

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4 For further discussion of this question, see: Balasubramiam, K. The main lines of cooperation among developing countries in pharmaceuticals. *World development*, 11: 281-287 (1983).
of the substance to which it is assigned. A substance can have only one international nonproprietary name, while it may have several trade names. Indeed, one commonly used drug is known to be marketed under more than seventy-five trade names.

The importance of formulating appropriate international nonproprietary names to be used for regulatory, labelling, scientific, and other purposes has been underlined by the international health community. The Sixth World Health Assembly, for instance, recognized¹ that the wide acceptance of nonproprietary names for drugs serves "the best interests of world health, assists the growth of international commerce in drug products and constitutes an additional basis for improved international relations".

International nonproprietary names are formulated by members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, following certain procedures and general principles that have been laid down.² Such names have to be distinctive in sound and spelling and should not be inconveniently long. There should be no room for confusion with names already in common use. The name of a substance belonging to a group of pharmacologically related substances must show this relationship. However, the name should be free from any anatomical, physiological, pathological, or therapeutic suggestion. In selecting an international nonproprietary name, every attempt is made to ensure that the proposed name does not conflict with any existing national trade marks. Interested parties are entitled to object to any proposed name on the basis that it is identical with or similar to a trade mark. In practice, however, such objections have been few and far between. Occasionally, an international nonproprietary name has been slightly modified in its application in a particular country on account of likely conflict with a registered trade name in that country. More than 5000 names have been formulated so far.

In order to reap the optimum benefits from the system of international nonproprietary names, it is essential that certain measures be taken at the national level. For instance, such names must be included in the records of national trade mark and patent registries, thus enabling national authorities to identify easily any possible conflict with trade mark applications. Measures have to be taken to prohibit the registration of trade marks that are in any way similar to an international nonproprietary name. To give effect to these measures, appropriate provision must be made in the legislation dealing with either pharmaceuticals or trade marks. It is of significance to note that Article 12 of the 1971 Convention on Psychotropic Substances specifically requires exporters of certain drugs to use international nonproprietary names. Moreover, the four schedules to the Convention have listed substances by their nonproprietary names.

¹ Resolution WHA 6.15 of May 1953.
The WHO certification scheme on the quality of pharmaceutical products moving in international commerce (Annex 3) requires Member States participating in the Scheme and who export drugs to ensure that, whenever possible, international nonproprietary names are used in the description of the composition of the product on the certificates and that as far as possible, such names appear on the labelling of the products to be exported.

Price Control

It is not sufficient to make drugs easily available; they should be reasonably priced too.

Price control of drugs has been tried in several countries with varying degrees of success. Provision can be made in the substantive law for orders to be made regarding the maximum prices of drugs. Price control can also be effected within the framework of a law dealing with price regulation in general. For instance, in Sri Lanka, the price of drugs was regulated under the Control of Prices Act.1 Price fixation and the enforcement of price control measures are matters that require manpower; in the absence of sufficient manpower it is not easy to have an effective price control system.

In the context of achieving economies of scale, pricing has, in some countries, become a relevant consideration when an application for the registration of a drug is considered. For instance, in Mali,2 no marketing licence for a pharmaceutical product can be given if several specialities having an identical or similar formula are already on the market and the introduction of the new speciality is not considered to be advantageous from either the therapeutic or the economic point of view.

Price control in relation to pharmaceutical raw material is not so common as price control of drugs. The recent Bangladeshi legislation, for instance, provides for the government to fix, by notification in the official gazette, the maximum price at which any pharmaceutical raw material may be imported or sold.3 It has been observed, however, that in practice it is not easy for the legal authority to intervene directly in the areas of transfer prices and of the sources of supply for subsidiaries of multinational companies.4

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1 Act No. 29 of 1950.
2 Decree No. 48 PG-RM of 18 March 1977.
3 Ordinance No. VIII of 1982.
CHAPTER 14

The effectiveness of legislation on pharmaceuticals

This chapter provides some guidelines on how to ascertain whether a drug law is operating effectively. In applying these guidelines, it needs to be borne in mind that evaluation of efforts in the health field presents particular problems since it is not always easy to measure what has been attained in a quantitative fashion. The process of evaluation depends to a considerable extent on the types of indicator and the criteria used and on the availability of adequate data. In the absence of appropriate indicators or criteria, pertinent questions have to be asked to elicit information on the basis of which conclusions can be drawn. In the area of health legislation, the process of evaluation has not achieved a high level of refinement. The guidelines offered here, therefore, are of a very general nature and need to be further refined and developed on the basis of field tests.

The effectiveness of any kind of legislation depends on several factors. The most important factor is that, at any given time, the legislative framework should be in tune with the policy relating to the subject area of the legislation. Changes in the policy need to be reflected in the legislation. The manner in which a law is implemented can reflect changes in policy.

The policy changes that need to be reflected in a drug law are not necessarily those related to pharmaceuticals. For instance, as part of the general health programme to extend the coverage of primary health care, new outlets or facilities might be established. If certain essential drugs can be made available at some of these outlets or facilities, the provisions in the law on pharmaceuticals will have to be examined with a view to finding out whether the law in fact permits the use of such outlets or facilities for these purposes. If not, appropriate amendments to the law will have to be introduced. To take another example, if a new category of health worker is recognized by the national health authorities, the legal provisions will have to be examined to ascertain whether it is permissible for such personnel to engage in any activity relating to or involving drugs.

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The responsibility for evaluating the effectiveness of a law on pharmaceuticals normally devolves on the institutional body, such as the regulatory authority, established by law for policy-making or implementation or both. Such a body also needs to engage periodically in some kind of self-evaluation to identify weaknesses in its policy-making and implementation activities. The body must devise its own systems to enable it to judge whether it receives sufficient feedback on how the law operates, whether it is possible to improve its operational effectiveness, etc.

The structure of the health care system and the nature of the legislative model determine to a great extent the types of indicator and criteria to be applied for purposes of evaluation. For instance, a country that is committed to a policy of rationalizing the availability of drugs must have an essential drugs list. Possible indicators of legal effectiveness would be: the existence and the periodical updating of a selected list having a legal basis; the authorization of channels of distribution and outlets; the authorization of personnel for prescribing and distribution, etc. The adequacy of the legal provisions and procedures can only be judged within the context of general indicators of the provision of health care, such as: availability; physical accessibility; economic and cultural accessibility; utilization of services; quality of care; availability of essential drugs throughout the year; and numbers of health workers in primary health care and at referral levels relative to the population.

The effectiveness of a law on pharmaceuticals can be measured more easily for certain elements or components than for others. For instance, the process of registration of drugs can be evaluated in relation to quantitative targets and time schedules. If the law provides for compulsory registration and if applications have to be processed within a particular time limit, examination of records will indicate whether the registration process is on schedule, ahead of schedule, or behind schedule. If it is behind schedule, the reasons for the delay need to be identified. If, for instance, one of the reasons is the inadequacy of details furnished by manufacturers, an appropriate amendment to the registration requirements can ensure that additional information is submitted at the outset, thus obviating the need for protracted correspondence and reconsideration. Evaluation is also possible in relation to qualitative dimensions, though it is more difficult than in the case of quantitative evaluation. When making an overall evaluation of the registration system, for instance, considerations of drug quality are more important from a medical than from a legal point of view.

The degree to which there is non-compliance with the law is indicative both of the need to take action against those responsible for non-compliance and of the desirability of identifying the causes of non-compliance. If technical defects in the law and operational problems in its implementation are causative factors, appropriate action should be taken to resolve such defects. Drug enforcement personnel should be required to submit periodic reports on their perception of how the law functions and the types of problem encountered. Such reports might provide information that is not otherwise available to those who are not actively involved in operational activities. These reports should give statistics on the insti-
tution and outcome of legal proceedings. Exchange of information regarding court proceedings and judgements can facilitate the work of both enforcement personnel and courts of law.

Evaluation processes must be considered an indispensable component of the work of both the regulatory authorities and the enforcement personnel, as a means of learning from past experience and improving current and projected activities.
Chapter 3 discussed three possible approaches to the effecting of substantive changes in drug legislation, namely:

(i) the revision and updating of existing legislation;
(ii) the replacement of existing legislation by entirely new legislation; and
(iii) the enactment of comprehensive legislation where none existed previously, by the consolidation and revision of certain sections in different existing laws, supplemented by new or additional provisions.

This annex looks at three national examples representative of each of the above approaches. The purpose is to highlight the situations in which recourse has been had to a particular method.

The three country case studies considered in this annex are India, Sri Lanka, and the Gambia. India introduced legislation in 1982 (Act No. 68) amending the Drugs and Cosmetics Act of 1940. The latter act had been amended from time to time but there had been a ten-year interval between the previous amendment and that of 1982. In the case of Sri Lanka, a new law was enacted in 1980 (Act No. 27) repealing the Food and Drugs Act of 1950. The 30-year interval between the two statutes did not witness any significant legislative interventions in respect of pharmaceuticals. The Gambia is representative of the third approach. The relevant provisions of the existing law were scattered among three separate pieces of legislation — the Druggists Act of 1894 and one regulation of 1897; the Dangerous Drugs Act of 1935; and the Customs Tariff Act of 1965. The Gambian example is also of interest because the new draft legislation was prepared by two outside experts, one from the World Health Organization and the other from the Ministry of Health of a Scandinavian country. They brought to bear on the drafting exercise several years of experience in the formulation of drug policies and the working of drug laws under different socioeconomic conditions. In February 1984, the Gambia enacted legislation based on this draft. For the purposes of this annex the draft submitted to the Government of the Gambia is considered so that attention can be focused on the rationale underlying some of the measures suggested by the mission.
Framework

The Drugs Act of 1940 was enacted during the colonial period. The Dangerous Drugs Act of 1930 was not affected by this legislation. Regulations under the Act of 1940 were enacted only around 1945 and the Act was implemented two years later when India gained independence. The Act was amended in 1955, 1960, 1962, 1964, 1972, and 1982. Cosmetics were brought within the purview of the legislation in 1962 and thereafter the legislation came to be known as the "Drugs and Cosmetics Act". Provision in respect of Ayurvedic (including Siddha) and Unani drugs was made in 1964. The Act empowered the Central Government to specify the substances coming within the definition of "drugs" and consequently contraceptives and disinfectants have been covered. The regulations contain a definition of homoeopathic medicines and provisions relating to their manufacture, sale, etc. The regulations also deal with poisonous substances. The Act provided for the establishment of a Drugs Technical Advisory Board, a Central Drugs Laboratory, and a Drugs Consultative Committee. It prohibited the importation, sale, or manufacture of any misbranded or adulterated drug or of a drug that is not of the standard quality; imports are permissible only under licence. The Act provided for rules and regulations to be made, and the Drugs and Cosmetics Rules of 1945, as amended from time to time, now run into more than 300 printed pages.

The Drugs and Cosmetics (Amendment) Act of 1982

The Drugs and Cosmetics (Amendment) Act¹ (hereafter referred to as the "amending Act" or "amending legislation") came into effect on 1 February 1983. For the present purposes only the amendments that relate to drugs and not those concerned with cosmetics or with Ayurvedic, Siddha, or Unani systems are considered. The scope of the Drugs and Cosmetics Act was extended to cover: preparations applied to the human body for the purpose of repelling insects; substances intended for use as components of a drug, including empty gelatin capsules; and devices intended for internal or external use in the diagnosis, treatment, investigation, or prevention of diseases in human beings or animals.

The amending Act added the category of "spurious drugs" to the categories of drugs deemed to be "misbranded" and "adulterated".

An important change introduced by the 1982 legislation is that the Central Government has been empowered to prohibit, if it is necessary or expedient to do so in the public interest, the import or manufacture, sale and distribution of a drug, if it is satisfied that:

¹ Act No. 68 of 1982.
(a) the use of the drug is likely to involve any risk to human beings or animals; or

(b) the drug does not have the therapeutic value claimed for it or it contains ingredients in quantities for which there is no therapeutic justification.

The amending legislation also provides for the Central Government to make rules not only after consultation with the Drugs Technical Advisory Board but also on its recommendation. Rules can be made, *inter alia*, for the cancellation or suspension of a licence for a contravention of the provisions of the Act dealing with import, manufacture, sale, and distribution of drugs, or if there has been non-compliance with the conditions subject to which the licence has been issued. Regulation-making power has been extended to cover prescription of the use of packing material that comes into direct contact with the drug.

In addition, the amending legislation introduced other changes, such as more severe penalties for non-compliance, and fees for the inspection of premises.

Comments

The Drugs and Cosmetics (Amendment) Act has more than 40 sections. The nature of the amendments is such, however, that they could conveniently be built into the existing framework. The legislation also has a history of having been expanded in scope from time to time and this latest amendment was thus in keeping with that tradition. The original legislation is 40 years old and there is a substantial body of case-law relating to its provisions. Since the legislation has been kept intact the case-law will continue to have the same binding force. The substantial body of rules enacted over the years will also remain intact.

Case Study No. 2 — Sri Lanka

Framework

Prior to the enactment of the Cosmetics, Devices and Drugs Act,¹ the Sri Lankan law on drugs was embodied mainly in the Food and Drugs Act, a statute modelled on the British legislation. Though Sri Lanka was independent in 1950 when the Food and Drugs Act was enacted, the British legal system, which had been applied for nearly 150 years in Sri Lanka, continued to have a persuasive influence on the law-making and judicial process. Besides the Food and Drugs Act, provisions relevant to drugs are also found in the Poisons, Opium and Dangerous Drugs Ordinance, the Penal Code, the Control of Prices Act, the Ayurveda Act, and the Customs Ordinance.

¹ Act No. 27 of 1980.
Amending legislation

The Cosmetics, Devices and Drugs Act of 1980 repealed the Food and Drugs Act. It established a Cosmetics, Devices and Drugs Authority and a Technical Advisory Committee. It provided for a system of licences for the manufacture, importation, sale, and distribution of drugs, and also, for the first time, for a system for the registration of drugs. In relation to various pharmacopoeias, it provided for standards to be enforced and laid down that labelling and advertising were to be confined to drugs that conformed to these standards.

Comments

The changes brought about by the Cosmetics, Devices and Drugs Act are of a very far-reaching nature. It would have complicated the structure of the Food and Drugs Act if such changes had been built into it. In these circumstances, a new piece of legislation was warranted.

Case Study No. 3 — the Gambia

Framework

The Druggists Act of 1894, the Dangerous Drugs Act of 1935, the Customs Tariff Act of 1965 contain various provisions relating to drugs. With the exception of dangerous drugs, which are covered by the Dangerous Drugs Act, the controls in respect of pharmaceuticals embodied in this legislation left much to be desired.

Proposed amendments

After a mission to the Gambia by two outside experts, a draft Medicines Act was presented to the national authorities in 1982. The mission surveyed available reports on the drug supply system in the country and interviewed officials who were responsible for the procurement and distribution of drugs. The views of private doctors and pharmacists were also sought. The amending legislation envisaged the repeal of the Druggists Act, and the amendment of the Dangerous Drugs Act, in the light of the two international drug control treaties. The Customs Tariff Act was to be left intact but customs authorities were to be furnished with information that would, inter alia, enable them to ban the import of certain drugs into the country. The draft Act used the expression “medicinal product” rather than “drug”. Articles that came within the definition of “medicinal product” could, by an order, be included or excluded from the purview of the legislation. The draft Act contemplated a system of drug registration and a licensing system for import, manufacture, distribution, sale, etc. A Medicines Board was to be instituted. The draft regulations contemplated con-
trols in respect of labelling, advertising, etc. The mission prepared detailed time schedules for the enactment and implementation of the legislation.

Comments

The nature of the amendments contemplated for the Gambia by the mission were such that they could not be incorporated into any of the existing laws. As noted earlier the existing framework was rudimentary. In drafting the legislation the mission took into account some of the formulae adopted by other countries. An example in point was the requirement relating to registration based on the Norwegian experience. On the basis of the proposed amendments a new Medicines Act, Act No. 2 of 1984, was enacted in the Gambia, repealing the Druggists Act which had been in operation for nearly 90 years.
Good practices in the manufacture and quality control of drugs¹

1. General considerations

   In the manufacture of drugs, overall control is essential to ensure that the consumer receives drugs of high quality. Haphazard operations cannot be permitted in the manufacture of substances that may be necessary to save life or to restore or preserve health.

   Difficulties will undoubtedly arise in establishing the necessary criteria for the manufacture of drugs that will meet established specifications and that can therefore be used with confidence. Recommended practices for the manufacture of drugs of desired quality are set forth below. Adherence to these practices, complementing the various control tests followed from the beginning to the end of the manufacturing cycle, will contribute substantially to the manufacture of consistently uniform batches of high-quality drugs.

   The manufacturer must assume responsibility for the quality of the drugs he produces. He alone can avoid mistakes and prevent mishaps by exercising adequate care in both his manufacturing and control procedures.

   The good practices outlined below should be considered as general guides; whenever necessary, they may be adapted to meet individual needs, provided the established standards of drug quality are still achieved.² They are intended to apply to the manufacturing processes (including packaging and labelling) used in the production of drugs in their finished dosage forms.

   Sometimes it occurs that several firms cooperate in the production (including packaging and labelling) of the finished dosage forms of drugs. It may also occur that a finished, packed, and labelled drug is repacked and/or relabelled, giving it a new designation. It should be pointed out that

² Additional recommendations specifically applicable to biological products are set forth in a number of sets of Requirements for Biological Substances adopted by the WHO Expert Committee on Biological Standardization and other WHO expert groups and published in the WHO Technical Report Series.
since such procedures constitute part of a manufacturing operation, they should be subject to the relevant requirements proposed below.

The requirements set forth herein are intended to apply primarily to preparations for human administration. However, equal attention should be given to quality in the manufacture of veterinary preparations.

2. Definitions

For the purposes of this document, the following definitions are adopted:

**Drug.** Any substance or mixture of substances that is manufactured, sold, offered for sale, or represented for use in (1) the treatment, mitigation, prevention, or diagnosis of disease, an abnormal physical state, or the symptoms thereof in man or animal; or (2) the restoration, correction, or modification of organic functions in man or animal.

**Manufacturing.** All operations involved in the production of a drug, including processing, compounding, formulating, filling, packaging, and labelling.

**Batch.** A quantity of any drug produced during a given cycle of manufacture. The essence of a manufacturing batch is its homogeneity.

**Batch number.** A designation (in numbers and/or letters) that identifies the batch and that permits the production history of the batch, including all stages of manufacture and control, to be traced and reviewed.

**Quarantine.** The status of a material that is set apart and that is not available for use until released.

**Quality control.** All measures designed to ensure the output of uniform batches of drugs that conform to established specifications of identity, strength, purity and other characteristics.

**"Half-finished" product.** Any material or mixture of materials that must undergo further manufacture.

3. Personnel

Experts responsible for supervising the manufacture and quality control of drugs should possess the qualifications of scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of (a) chemistry (analytical chemistry, biochemistry, etc.); (b) chemical engineering; (c) microbiology; (d) pharmaceutical sciences and technology; (e) pharmacology and toxicology; (f) physiology and histology; and (g) other related sciences. They should also have adequate practical experience in the manufacture and quality control of drugs. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and
practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of drugs.

Such experts should preferably not have any interests outside the manufacturer’s organization that (a) prevent or restrict their devoting the necessary time to their assigned responsibilities or (b) may be considered to entail a conflict of financial interest. Finally, they should be given full authority and the facilities necessary to carry out their duties effectively.

In addition to the experts noted above, an adequate number of technically trained personnel should be available to carry out the manufacturing and quality control operations in accordance with established procedures and specifications. All personnel should be motivated towards the establishment and maintenance of high quality standards.

4. Premises

4.1 General

Drugs should be manufactured, processed, packaged, labelled, and tested in premises that are suitable for these purposes.

In determining the suitability of premises regard should be paid to:

(1) the compatibility of other manufacturing operations that may be carried out in the same or adjacent premises;

(2) the adequacy of the working space, which should allow orderly and logical placement of equipment and materials so as to (a) minimize the risk of confusion between different drugs or their components, (b) control the possibility of cross-contamination by other drugs or substances, and (c) minimize the risk of omission of any manufacturing or control step;

(3) those physical aspects of the premises that could affect the quality and safety of products: buildings should be so designed and constructed as to prevent the entry of animals and insects; interior surfaces (walls, floors and ceilings) should be smooth and free from cracks, should not shed particulate matter, and should permit easy cleaning and if necessary disinfection;

(4) lighting, heating, ventilation and, if necessary, air conditioning, required to maintain a satisfactory temperature and relative humidity that will not adversely affect the drug during manufacture and storage, nor the accuracy and functioning of laboratory instruments.

4.2 Storage areas

The suitability of storage areas cannot be strictly specified in a manner that meets all possible contingencies. However, the following principles should be observed:
(1) storage areas should provide adequate space, suitable lighting, and should be arranged and equipped to allow dry, clean, and orderly placement of stored materials and products, whenever necessary under controlled conditions of temperature and humidity;

(2) such areas should provide for suitable and effective separation of quarantined and other materials and products;

(3) special and segregated areas should be available for storage of:

   (a) substances presenting special risks of fire and explosion;

   (b) highly toxic, narcotic, and other dangerous drugs (these areas should be adequately protected against theft);

   (c) rejected and recalled materials and products.

4.3 Special

For special purposes, such as the manufacture of drugs that are intended to be sterile but cannot be sterilized in their final containers, separate enclosed areas, specifically designed for the purpose, should be provided. These areas should be entered through an air-lock and should be essentially dust-free and ventilated with an air supply through bacteria-retaining filters giving a pressure higher than in adjacent areas. Such filters should be checked for performance on installation and periodically thereafter. All surfaces in manufacturing areas should be designed to facilitate cleaning and disinfection.

Routine microbe counts of the air in the areas described above should be carried out before and during manufacturing operations. The results of such counts should be checked against established standards, and adequate records of the counts should be maintained.

For the manufacture of drugs that can be sterilized in their final containers, the requirements given above are considered essential, with the exception of mandatory sterilization of air supplies. The design of areas used for this purpose should preclude the possibility that products intended for sterilization could be mixed with, or taken to be, products already sterilized. This may conveniently be effected by the use of double-ended sterilization apparatus opening into separate and non-communicating areas.

5. Equipment

Manufacturing equipment should be designed, placed, and maintained in such a way as to:

(1) be suitable for its intended use;

(2) facilitate thorough cleaning wherever necessary;

(3) minimize any contamination of drugs and their containers during manufacture; and

(4) minimize the risk of confusion or the omission of a processing step such as filtration or sterilization.
Operating conditions within an apparatus used to sterilize products should be monitored by means of recording devices, which should be initially calibrated and checked at approved intervals by approved methods. Suitable standardized microbiological indicators may be used to demonstrate the adequacy of the sterilization process.

Manufacturing equipment and utensils should be thoroughly cleaned and, when necessary, sterilized, and should be maintained in accordance with specific written directions. When indicated, all equipment should be disassembled and thoroughly cleaned, to preclude the carry-over of drug residues from previous operations. Adequate records of such procedures should be maintained.

Equipment used for aseptic filling should be checked at suitable intervals by microbiological methods. Weighing and measuring equipment used in production and quality control should be calibrated and checked at suitable intervals by appropriate methods. Adequate records of such tests should be maintained.

6. Sanitation

Manufacturing premises should be maintained in accordance with the sanitary standards issued by the appropriate health authority. They should be clean and free from accumulated waste, orderly, and free from vermin. A written sanitation programme should be available, indicating:

(1) areas to be cleaned, and cleaning intervals;
(2) cleaning procedures to be followed and, if necessary, equipment and materials to be used for cleaning; and
(3) personnel assigned to and responsible for cleaning operations.

Eating, smoking, and unhygienic practices should not be permitted in manufacturing areas.

Sufficient, clean, well-ventilated toilet facilities, including facilities for hand-washing and rooms for changing clothes, should be available near working areas for the use of manufacturing personnel.

7. Starting materials

An inventory should be made of all starting materials to be used at any stage in the manufacture of drugs, and records should be kept of the supplier, the origin (if possible), date of receipt, date of analysis, date of release by the quality control department, and their subsequent use in manufacture.

All such materials must be:

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1 This may be accomplished by conducting normal filling operations using suitable sterile liquid bacteriological media or other media suitable for dry powder filling, as the case may be, taking into consideration the risks of microbiological contamination of the equipment.
(1) identified, and their containers examined for damage;
(2) properly stored in quarantine;
(3) properly sampled by the quality control department;
(4) tested for compliance with requirements (all materials should be marked to indicate that they are undergoing testing); and
(5) released from quarantine by the quality control department by means of written instructions.

Starting materials that are accepted or approved should be properly and conspicuously labelled as such, and should then be transferred, if necessary, to areas designated for the storage of such materials.

All rejected starting materials should be conspicuously identified as such, and should be destroyed or returned to the supplier as soon as possible.

8. Manufacturing operations

Manufacturing operations and controls should be carried out under the supervision of experts, as specified in section 3.

8.1 Cleanliness

Before any manufacturing operation is begun, a check should be made to ensure that all apparatus and equipment to be used in the operation has been cleaned and/or sterilized (see section 5).

8.2 Equipment and containers

The contents of all vessels and containers used in manufacture and storage between manufacturing stages must be identified by conspicuously placed and clearly legible labels, bearing the name and/or identification code of the processed materials and the necessary batch identification data. Similar labels should be attached to mechanical manufacturing equipment during its operation.

8.3 Precautions against contamination and confusion (mix-up)

All manufacturing operations should be confined to separate areas intended for such purposes, with complete equipment used exclusively in those areas, or measures should be taken to ensure that neither cross-contamination nor confusion (mix-up) can occur.1

In manufacturing areas, clean working garments should be worn over, or in place of, street clothing.

The manufacture of drugs intended to be sterile should be performed in areas specially designed and constructed, as indicated in section 4.3.

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1 The simultaneous manufacture, in adjacent areas that are not physically separated, of drugs that are similar in appearance should be avoided.
Whenever the different operations are not physically separated, and there is a possibility that unsterilized and sterilized products might be confused, all containers of batches of products for sterilization should bear a clear indication of whether or not their contents have been sterilized.

Products that undergo sterile operations should be protected from contamination by using methods such as laminar-flow techniques, and by ensuring that personnel wear clean, sterile gowns, head coverings, masks, rubber gloves, and shoe coverings. Before dressing and entering sterile areas, personnel must wash their hands with a suitable disinfectant.

All dust-producing operations involving highly potent substances, particularly antibiotics, should be conducted in confined areas that are provided with adequate exhaust systems or that are maintained under appropriate pressure, so as to prevent cross-contamination. Adequate precautions should be taken to prevent the recirculation of contaminated air.

8.4 Manufacturing personnel

No person known to be affected with a disease in a communicable form, or to be the carrier of such a disease, and no person with open lesions on the exposed surface of the body, should be engaged in the manufacture of drugs. Manufacturing personnel should undergo periodic health checks. In order to prevent any impairment of health caused by the handling of hazardous or potent materials, manufacturing personnel should, whenever necessary, wear protective clothing, shoes, headgear, dust masks, etc., and such protective clothing should remain in the area in which it is used. In some instances, it may be necessary to have restrictions on the movement of personnel to and/or from special working areas.

8.5 Documents relating to manufacturing procedures

Documents relating to manufacturing procedures should be prepared for each drug under the direct supervision of experts (see section 3) who have the necessary authority. They should contain at least the following information for each drug:

1. its name and dosage form;
2. a description or identification of the final container(s), packaging material(s), and labels and, where applicable, of the closure(s) to be used;
3. the identity, quantity, and quality of each starting material to be used, irrespective of whether or not it appears in the finished drug (the permissible excess ("overage") that may be included in a formulated batch should be indicated);

Such documents should not be handwritten nor contain handwritten amendments or comments. When necessary they should be rewritten and all outdated instructions withdrawn, to avoid the possibility of re-use. They should be suitable for copying in a manner that avoids any possibility of a transcription error.
(4) the theoretical yields to be expected from the formulation at different stages of manufacture and the permissible yield limits;

(5) detailed instructions for, and precautions to be taken in, manufacture and storage of the drug and of “half-finished” products; and

(6) a description of all necessary quality control tests and analyses to be carried out during each stage of manufacture, including the designation of persons or departments responsible for or charged with the execution of such tests and analyses.

8.6 Batch manufacturing records

Manufacturing records must provide a complete account of the manufacturing history of each batch of a drug, showing that it has been manufactured, tested, and analysed in accordance with the manufacturing procedures and written instructions described in section 8.5. A separate batch manufacturing record should be prepared for each batch of drug produced, and should include the following information:

(1) name and dosage form;
(2) date of manufacture;
(3) batch identification;
(4) complete formulation of the batch (see section 8.5 (3));
(5) the batch number (or analytical control number) of each component used in the formulation;
(6) the actual yield obtained at different stages of manufacture of the batch as compared with the theoretical yield (see section 8.5 (4));
(7) a duly signed record of each step followed, precautions taken, and special observations made throughout the manufacture of the batch;
(8) a record of all in-process controls followed and of the results obtained;
(9) a specimen of the actual coded label used;
(10) identification of packaging materials, containers, and, where applicable, closures used;
(11) signature of the expert responsible for the manufacturing operations, and the date of his signature;
(12) an analytical report showing whether the batch complies with the prescribed specifications for the drug, dated and duly signed by the responsible expert;
(13) a record of the decision regarding the release or rejection of the batch by the quality control department (see section 10.1 (5)); and
(14) if the batch is rejected, a record of its disposal or utilization.

8.7 Maintenance of batch manufacturing records

For reference purposes, all batch manufacturing records should be retained for a specified period.
9. Labelling and packaging

Labelling and packaging materials, including leaflets, should be stored and handled in such a way as to ensure that labels, packaging materials and leaflets relating to different products do not become intermixed. Access to such materials should be restricted to authorized personnel.

Prior to packaging and labelling of a given batch of a drug, the manufacturing and control records specified in section 8.6 should show that the batch has been duly tested, approved, and released by the responsible quality control expert. Prior to being issued, all labels for containers, cartons, and boxes and all circulars, inserts, leaflets, etc., should be examined and released as satisfactory for use by the designated person(s) (see section 10.1 (4)).

To prevent packaging and labelling errors a known number of labelling and packaging units should be issued and, if required, coded. Such issuance should be made against a written, signed request that indicates the quantity and types required.

Upon completion of the packaging and labelling operation, a comparison should be made between the number of labelling and packaging units issued and the number of items labelled and packaged plus the number of units not used. All coded unused units should be destroyed. Any significant or unusual discrepancy in the numbers should be carefully investigated.

All finished drugs should be identified by labelling that should bear, clearly indicated, at least the following information:

1. the name of the drug;
2. a list of the active ingredients, showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight or volume;
3. the batch number assigned by the manufacturer;
4. the expiry date, if required (see section 10.1 (8));
5. any special storage conditions or handling precautions that may be necessary;
6. directions for use, and warnings and precautions that may be necessary; and
7. the name and address of the manufacturer or the person responsible for placing the drug on the market.

10. The quality control system

10.1 Quality control department

Every manufacturing establishment must have a quality control department supervised by a suitably qualified expert directly responsible to management but independent of other departments. The quality control department should control all starting materials, monitor the quality
aspects of manufacturing operations, and control the quality and stability of drugs.

The quality control department should have the following principal duties:

1. to prepare detailed instructions, in writing, for carrying out each test and analysis;
2. to release or reject each batch of starting material;
3. to release or reject “half-finished” products, if necessary;
4. to release or reject packaging and labelling materials and the final containers in which drugs are to be placed;
5. to release or reject each batch of finished drug that is ready for distribution;
6. to evaluate the adequacy of the conditions under which starting materials, “half-finished” products, and finished drugs are stored;
7. to evaluate the quality and stability of finished drugs and, when necessary, of starting materials and “half-finished” products;
8. to establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions;
9. to establish, and when necessary revise, control procedures and specifications; and
10. to be responsible for the examination of returned drugs, to determine whether such drugs should be released, reprocessed, or destroyed. Adequate records of the disposition of such drugs should be maintained.

In order to fulfil its responsibilities, the quality control department should take samples (e.g., of starting materials and finished drugs), according to established procedures. The samples should be properly labelled, and portions should be kept for future reference.

The quality control department should maintain adequate analytical records concerning the examination of all samples taken. Such records should include:

(a) the result of every test performed, including observations and calculations, relating to compliance with the established specifications;
(b) the source of the specifications used;
(c) the signature(s) of the person(s) who performed the quality control procedures; and
(d) a final review, the decision taken, and a dated endorsement by a duly authorized expert.

10.2 Quality control laboratory

The quality control department should have a laboratory available to it. The laboratory should:
be adequately staffed and fully equipped for performing all quality control tests and analyses required during and after manufacture;¹
(2) be supervised by a qualified expert (see section 3).

11. Self-inspection

In order to maintain strict adherence to all manufacturing procedures and prescribed controls, it may be advisable for a firm to designate an expert or a team of experts to conduct regularly scheduled inspections of its overall manufacturing and control operations. However, this should not be taken to mean that any firm that exercises self-inspection should be exempt from the official inspections required by the laws and regulations of the country in which it is located.

12. Distribution records

Adequate records should be maintained of the distribution of a finished batch of a drug in order to facilitate prompt and complete recall of the batch if necessary.

13. Complaints and reports of adverse reactions

Reports of injuries or adverse reactions resulting from the use of a drug should be forwarded to the appropriate authorities. Complaints regarding the quality of a drug, including any change in its physical characteristics, must be thoroughly investigated. If they prove well-founded, appropriate measures must be taken as soon as possible. The measures taken should be recorded and filed with the original complaint.

¹ If animal tests are necessary, the animals should be given adequate quarters and care (for further information, see WHO Technical Report Series, No. 323, 1966, pp. 14, 16). The use of outside independent laboratories may be advisable for specialized and complex analytical and biological procedures that require the use of costly equipment and that can be performed only by technicians with specialized training. Such laboratories should be adequately staffed and fully equipped to perform such analyses.
Certification scheme on the quality of pharmaceutical products moving in international commerce

Part I — Certification of Pharmaceutical Products

1. For the purpose of this Certification Scheme "pharmaceutical product" means any medicine in its finished dosage form, intended for human use, that is subject to control by legislation in the exporting Member State and in the importing Member State.

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

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

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

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

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

4. If certificates of individual batches of products covered by a Certificate of Pharmaceutical Products are required, such certificates could be

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issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of Pharmaceutical Products, and a statement that the batch conforms either to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, as the case may be, to published specifications, or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis, and other data.

Part II — Exchange of Information

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

   (a) information on the implementation of the Requirements for Good Practices in the Manufacture and Quality Control of Drugs as recommended by the World Health Organization;¹
   (b) information on controls of the product as exercised by the competent authority of the exporting Member State;
   (c) the names and functions of the persons designated to sign certificates of individual batches of the product to be exported.

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

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

¹ It is realized that in some countries this may require the consent of the manufacturer.
ANNEX 3

Part III — Participating Member States

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

2. Exporting Member States participating in the certification scheme shall ensure that:

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

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

   (c) the competent authority is empowered to conduct appropriate investigations to ensure that manufacturers conform to the requirements referred to in (b), including, for example, the examination of records and the taking of samples;

   (d) the inspectors of the services of its competent authority have appropriate qualifications and experience.

3. Exporting Member States participating in the certification scheme should, whenever possible, ensure that the international nonproprietary names, whenever available, are used in the description of the composition of the product on the Certificates and, as far as possible, appear on the labelling of pharmaceutical products to be exported under the certification scheme.
CERTIFICATE OF PHARMACEUTICAL PRODUCT(S)\textsuperscript{1}

Name and dosage form of product: ..............................................
Name and amount of each active ingredient: ..........................

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

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

It is certified that:

\begin{itemize}
\item \textbf{This product has been authorized to be placed on the market for use in this country.}
\end{itemize}

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

\begin{itemize}
\item \textbf{This product has not been authorized to be placed on the market for use in this country for the following reasons:}
\end{itemize}

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

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

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

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

\textsuperscript{1} This form may be adapted to cover several products from the same manufacturer.

\textsuperscript{2} Use, whenever possible, international nonproprietary names (INN) or national non-proprietary names.
Explanatory Notes

Certificate of Pharmaceutical Product(s)

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

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

Batch certificates

If certificates of individual batches of products covered by a Certificate of Pharmaceutical Products are required such certificates could be issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of Pharmaceutical Products and a statement that the batch conforms either to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, where appropriate, to published specifications or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis, and other data.

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1 See Annex 2 of the present publication.
Note on clinical trials

The performance of clinical trials may or may not be a precondition for the registration of imported drugs. It is usually insisted upon as a condition for the introduction of locally manufactured new drugs and certain new drugs that are to be imported for the first time. Clinical trials entail prescreening procedures and compliance with sound medical and ethical principles. Instead of requiring clinical trials to be undertaken in an importing country, drug regulatory agencies may evaluate results of clinical trials and tests as well as post-marketing data from the country of manufacture and from a number of other countries where the drug is being used. For that reason, repetition of clinical trials may be required only when they are essential on account of climatic and genetic factors or the particular epidemiological or nutritional conditions in the country.¹

Different countries have adopted different principles for regulating clinical trials. Inasmuch as “drug toxicity is protean in its manifestations, unpredictable in its occurrence and commonly resistant to detection”² experimenting with new drugs of which relatively little is known is a hazardous exercise. Animal studies may not reveal all important toxic effects, and it is inevitable that human subjects should be used for biomedical research. Research studies, involving as they do the administration of substances about whose biological activity relatively little can be predicted, entail some element of risk. As long ago as 1966, a WHO Scientific Group remarked that this element of risk “cannot be avoided by the most careful and exhaustive scientific study of the drug before it is used”.³ Despite advances in pharmacology and toxicology, this observation is as true today as it was then. The inherent risks are more or less the same wherever biomedical research of a general nature is carried out. For this reason, attempts have been made to set out certain basic principles that must be adhered to whenever biomedical research involving human subjects is carried out. These principles, which cover a wide range of matters, can be divided into two categories, namely:

(a) medical or scientific principles; and
(b) ethical principles.

The considerations underlying these principles have, over the years, generated a considerable amount of research and writing. In the present context, it is not possible to do justice to a topic so rich in its literature. What is attempted here is to advert to some of the more salient issues on which there has been a certain degree of consensus throughout the world. National legislation and codes of ethics vary in their comprehensiveness and in their depth of treatment of these issues, but examination of them is suggestive of the range of principles and guidelines to be accorded sanction. The fundamental principles will, in general, be of universal application, subject to the requirements of individual legal systems.

The medical or scientific and ethical principles that have been laid down represent a compromise between the need to use human subjects for testing biologically active substances that have the potential to benefit mankind and the need to conduct experiments and trials in a manner that preserves human dignity.

In the international sphere, the Nuremberg Code of 1947 was the first instrument of its kind to set out certain principles. In 1964, the World Medical Association adopted a Declaration, which later came to be known as the Declaration of Helsinki. In 1975, the Declaration was revised by the same Association. This Declaration superseded the Nuremberg Code and is now widely accepted as the basic document in its field. Some countries have made specific reference to these documents. For instance, the Argentinian legislation requires clinical trials to be conducted in accordance with the provisions of the Nuremberg Code and the revised Helsinki Declaration.

The medical and scientific principles relevant to biomedical research involving human subjects are structured on the premise that the laboratory studies of the efficacy of the drug have demonstrated that “there is a real therapeutic interest sufficient to justify the trial of the drug in man” and that “the intended purpose of the drug is important”. The best safeguard is to place the investigations “in the hands of those experienced in pharmacology and toxicology”. The importance of the objective must be “in proportion to the inherent risk to the subject” and there has to be a

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1 For a further discussion see: Levine, R. J. Ethics and regulation of clinical research. Baltimore, Urban and Schwarzenberg, 1981.
4 See WHO Chronicle, 30: 360-362 (1976).
5 Resolution No. 858 of 10 April 1979.
“careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others.”¹ A paramount consideration to be borne in mind before, during, and after any research involving human subjects is the respect for the right of the subject to safeguard his integrity. The health and safety of the subject must take precedence over the interests of science and society. The continuation of a project needs to be reconsidered in the event of unanticipated jeopardy to the well-being of the subject. The research project must be carefully formulated. Its details must be set out in a protocol, which should be reviewed by an independent ethical committee. Some countries have provided for national committees. For instance, Costa Rica enacted a Decree² in 1972 establishing an Institutional Committee on Medical Investigations Involving Human Subjects. The Committee comprises four persons representing the Ministry of Public Health, the University of Costa Rica, the Association of Physicians and the Association of Pharmacists, and must express an opinion on the desirability or otherwise of any proposed trial.

Before a clinical trial is conducted, those who are responsible for it must ensure that provision has been made for insurance to compensate the subject if he or she suffers harm as a result of receiving the drug.³ The identification of the causal link between the administration of a drug and a particular complication is often difficult. Commercial insurance is more easily available in respect of healthy volunteers than in respect of sick persons.

Ethical issues loom large in any doctor–patient relationship and when it comes to clinical experimentation these issues assume an even more significant dimension. The consent of the subject is “a crucial element in all national and professional arrangements made to ensure the ethical conduct of research involving human subjects”.⁴ The subject must be informed of “the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail”.¹ Consent may be regarded as valid only if the subject has brought to bear on the decision a free mind not influenced by considerations of fear, threat, influence or money. Different requirements regulate the manner in which consent should be obtained. In respect of certain categories of subjects, such as minors, the consent of another person, such as a parent or a guardian, might be necessary. In community-based research involving groups of individuals, obtaining consent is more difficult and appropriate channels

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¹ Declaration of Helsinki.
² Decree No. 2393-SP PS of 16 June 1972.
must be identified. The privacy of the subject must be respected and a certain degree of confidentiality in respect of the identity of the subject must be observed, even in the publication of the research data. Those who conduct clinical trials must remain responsible for the health and well-being of the subject during, and for a reasonable time after, the trial. If the hazards are found to outweigh the potential benefits, the trial should be terminated, notwithstanding that the subject or subjects may desire the investigations to continue.
Quality assurance in pharmaceutical supply systems

The main components of quality assessment and assurance are the legal base, the regulatory elements, and the technical elements.

Legal base

The legal framework should form an integral part of general drug legislation and should provide the necessary authority to develop appropriate regulations pertaining to the manufacture, importation, and distribution of pharmaceutical products and, possibly, of pharmaceutical raw materials. Responsibility for the development of guides, norms, and administrative regulations may be delegated to a drug control agency. There are wide differences between countries in their legal approach, depending on whether the administrative structure is centralized or decentralized.

Regulatory elements

The aim of the regulations is to ensure that all manufacturers comply with good manufacturing practices and, at the distribution level, that the quality of all pharmaceutical products has been properly assessed. This applies especially to imported items. Procedures must exist for adequate control over the transport, storage, and rotation of supplies and for the recall, if necessary, of unsatisfactory products.

To facilitate adequate national control of drug supply systems, authority should be vested in the ministry responsible for health matters. This would allow a drug control agency to be set up and the necessary administrative and regulatory procedures to be developed, including drug

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notification and authorization or registration. The agency should have an expert staff, fully trained in the carrying out of drug quality surveillance. To perform this task adequately, it should be supported by inspection and laboratory services. The inspection services act as the field arm of the agency and are responsible for verifying that manufacturing and distributing firms, as well as retail and dispensing outlets, comply with the regulations. The control laboratory carries out tests and assays to establish whether drugs conform to the specifications claimed for them. Its type and size will be determined by such factors as the nature of the pharmaceutical supply system, the extent of local drug production, and the volume of imports. Both in the inspection services and in the laboratory services there is scope for international cooperation, and the creation of a regional control laboratory may be feasible.

Technical elements

From the technical point of view, drug quality is achieved by strict adherence to the specifications. These comprise a set of properly selected standards accompanied by methods of analysis designed to be used to assess the integrity of drugs and starting materials and to ensure that all batches of a drug (and dosage forms) are of uniform quality. Quality specifications may be of a public nature, in which case they are usually contained in a pharmacopoeial monograph and are stated in terms that permit the objective evaluation of product quality by any interested party. Many specifications, however, are either contained in an application for an authorization or registration or exist as the manufacturer's own specifications. As such specifications are not usually subject to public disclosure, interested parties have to depend on the licensing authorities or the manufacturer for assurance that they are adequate and that they are being met.

In certain circumstances, e.g., where no well equipped laboratories exist, simplified tests may be used to verify the identity of a drug and check its purity. If a product fails such basic tests, it should not be used until its quality has been established by a full analytical examination.

To ensure that pharmaceutical products satisfy the established standards of drug quality, it is essential that the principles laid down in Good practices in the manufacture and quality control of drugs\(^1\) should be followed. These requirements may be adapted to meet national needs and manufacturers may select those parts relevant to their production range. In all cases, however, the documents relating to manufacturing procedures must contain data concerning each starting material, as well as detailed instructions for and precautions to be taken in the manufacture of the drug.

Pre-marketing quality assessment

Before permission is given for a drug to be placed on the market, it must satisfy certain quality requirements established by the competent health authorities — usually the drug control agency. The least resource-intensive way of obtaining information about drugs offered for sale in a country is through a notification procedure. In addition to the name of the drug and that of the manufacturer, the information requested may include the nonproprietary names for active substances, the composition, and the pharmacological classification. In many countries, some or all drugs are subject to an authorization procedure before they are marketed. This procedure may vary in stringency but almost always includes inspection of the manufacturer and verification of product quality by analysis. If registration is required before permission is given to market a drug, the procedures may include evaluation of the safety and efficacy of the drug as well as an assessment of the manufacturing processes. When a product has already been used extensively and sufficient experience exists to demonstrate the safety of the active ingredient in similar types of preparation, the administrative requirements may be reduced to a declaration of manufacturing data and pharmaceutical quality specifications.

Drug quality surveillance during marketing

Drug quality surveillance is facilitated if lists of nonproprietary names are established for all pharmaceutical substances on the market, with indications of any trade names. WHO is carrying out a programme on the standardization of drug nomenclature and regularly publishes lists of International Nonproprietary Names for pharmaceutical substances.

Control authorities should be informed of the places in which drugs are manufactured, stored and distributed, the names of the persons responsible for marketing in each manufacturing establishment, the nature of the distribution mechanism, and the destination of the products. Manufacturing premises must be regularly inspected to ensure that good manufacturing practices are being followed, special attention being paid to any alterations in the master formula and manufacturing procedures. For certain types of drugs, such as those that are potent but highly labile, a system of batch control, or batch certification, may be used, the batch being released only after a random sample has been shown by a government drug control laboratory to be of satisfactory quality. Once the quality level has been demonstrated to be sufficiently uniform, batch control can usually be phased out.

For the surveillance of imported drugs, the WHO certification scheme on the quality of pharmaceutical products moving in international commerce will provide the control authorities with valuable data. The scope of the information required may vary according to the category of the drug and the control procedure adopted by the importing country. It is important that proper administrative procedures should be worked out to make sure that, at the port of entry, consignments of drugs are stored under
suitable conditions and for as short a time as possible, in order to prevent deterioration. Pharmaceutical officers at customs posts can help in this control activity and can ensure that each shipment is accompanied by the requisite information.

Every pharmaceutical product has a shelf-life during which its quality may be expected to remain within acceptable limits, provided that adequate conditions of storage are maintained during all phases of distribution. In regard to quality surveillance at this stage, therefore, particular attention must be paid to storage facilities and transport conditions. For drugs known to have a short shelf-life, the expiry date should be stated clearly on the labels. The indication of the date of manufacture would further facilitate the quality surveillance of pharmaceutical products during distribution.