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CHAPTER 6

Pharmaceutical legislation and regulation

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SUMMARY

Realistic and effective laws and regulations are needed for the pharmaceutical sector because—

- Pharmaceuticals concern the whole population
- Many parties are involved: patients, health providers, manufacturers, and salespeople
- Serious consequences, including injury and death, can result from the lack or misuse of medications
- The consumer has no way to determine product quality
- Informal controls are insufficient

Countries may choose to develop new legislation or to revise existing laws. When starting afresh, it is useful to prepare a general law. Models exist, and expert assistance is readily available. After the law is passed, regulations made under it can bring its various provisions into operation, one by one, as the necessary resources and experience are acquired.

In drafting or revising legislation, a country should—

- Inventory the laws and regulations already in force
- Determine what type of legislative instrument is required
- Involve both legal and health experts
- Keep all interested parties informed

National drug legislation generally includes provisions relating to the manufacturing, importing, distribution, marketing, prescribing, labeling (including language), dispensing, and sometimes pricing of pharmaceutical products, as well as the licensing, inspection, and control of personnel and facilities. A regulatory authority is usually established for administrative control. Medicine registration is often a major element in legislation, to ensure that individual products meet the criteria of efficacy, safety, and quality.

Countries that need to introduce comprehensive legislation can seek guidance from the experiences of others and from WHO (2001a) guidelines.

6.1 The role of pharmaceutical legislation and regulation

The role of pharmaceuticals has become more prominent on international agendas as health indicators have been increasingly linked with a country's successful development. In addition, the legal and economic issues that surround pharmaceuticals have become more complex and politicized because of the increase in global trade.

Why pharmaceutical laws and regulations are necessary

The use of ineffective, poor-quality, or harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines, and sometimes death. It also undermines confidence in health systems, health professionals, pharmaceutical manufacturers, and distributors. To protect public health, governments need to approve comprehensive laws and regulations and to establish effective national regulatory authorities to ensure that the manufacture, trade, and use of medicines are regulated appropriately and that the public has access to accurate information on medicines.

Differences between pharmaceutical laws, regulations, and guidelines

Laws today are usually written in fairly general terms to meet present and possibly future needs. Laws usually have

language that enables the government to issue regulations based on the law. Passing new laws may require a lengthy process, with the country's legislative branch giving final approval. Regulations can be passed more rapidly and simply than laws, sometimes requiring, for example, only the approval of a single government minister on the advice of experts. They can also be altered more easily. After approval, a regulation has the same power as the law itself. Guidelines, which do not carry the force of law, can be more easily modified and updated and offer informal information on what the government's thinking is regarding the best way to implement regulations. Following guidelines will help avoid misinterpretation of and facilitate compliance with laws and regulations.

Pharmaceuticals involve many parties, including patients, doctors, other health workers, salespeople, and manufacturers. The field also involves important risks: people can suffer or die not only from a lack of medicines, but also from drugs that are impure, wrongly prescribed, or used incorrectly. Thus, it is easy to see why laws and regulations are needed. However, some argue that medicines—like many other commodities—should be subject only to the control of the ultimate user. But medicines are indeed different, as discussed in Chapter 1.

Additionally, informal controls are insufficient: charlatanism or quackery (that is, the deliberate sale of remedies known to be worthless) is centuries old, and firm action may be needed to put a stop to it; however, as discussed later in the chapter, the Internet presents new challenges in

controlling deceitful drug promotion. Counterfeiting, also, has been on the rise in developed and developing countries. U.S. customs officials, for example, report that pharmaceuticals are one of the fastest-growing categories of counterfeit goods coming into the country illegally. Pharmaceuticals accounted for 10 percent of total seizures in 2008 to become the third-largest category, compared to 6 percent in 2007 (Mui 2009).

The approach to pharmaceutical regulation should not be simply punitive: rules creating a positive situation tend to be more effective. Finally, laws and regulations are effective only to the extent that they meet society's needs.

Evolution of policy and law

There may be a long preparatory period before the sort of consensus develops that can form the basis for a law. It is sometimes preferable to work for a while with informal agreements among parties or with government guidelines, so that generally accepted rules of behavior can develop in practice; the law then serves to confirm and formalize them (see Country Study 6-1).

Whether or not a national drug policy exists, countries need effective, enforceable legislation and regulation. These legislative acts may take the form of a single national drug law that deals with all the issues or a series of complementary laws, each introduced when the time is right. In some countries, certain aspects of the pharmaceutical sector are governed by national laws, and other aspects, such as pharmacy and medical practice, are governed by state or provincial laws. This chapter focuses on a single, comprehensive drug law at the national level. Most of the issues discussed are also applicable in situations where legal responsibility is divided between national and state or provincial governments.

A law on medicines must, first and foremost, clearly define what all the parties—manufacturers, doctors, pharmacists—are required to do, so that no serious misunderstanding is possible. Medicine registration laws and regulations, for example, make clear what a manufacturer needs to do to obtain a license to sell a product. They define how a registration agency should assess both the manufacturer and the product to determine if they meet society's needs.

A good law also creates administrative bodies to put rules into practice—for example, a national drug regulatory authority with broad competence, or separate organs to deal with the various aspects of pharmaceutical regulation such as practice of pharmacy, inspection of factories, and advertising of medicines.

Trying to achieve too much, too quickly, can be tempting. It took more than a hundred years for pharmaceutical policies and laws to evolve to current levels in the industrialized world. Sensible questions to ask are—

- What are the most important goals to achieve within five, ten, and fifteen years?
- What means are available to achieve them?
- In which order can they best be tackled?
- What help is available?

The answers to these questions provide a good starting point in developing both policies and the laws needed to support them.

Laws and regulations are intended to be used together to achieve their objective. It is appropriate to begin with passing a broad law, emphasizing the requirement that pharmaceutical products be safe and effective. The various provisions of the law are then brought into operation through regulation, step by step, addressing the most important things first. For instance, in resource-constrained countries, setting up a new pharmaceutical distribution system may be urgently necessary, but pharmaceutical registration can wait for several years, while procuring essential medicines in the meantime through reputable channels where product quality is controlled.

Globalization and harmonization

Laws and regulations evolve within countries over time, but in recent years, the trend has been toward the globalization of pharmaceutical issues, which affects national legislation. This globalization, exemplified through changes in international trade, patent protection, and pricing, has resulted in a number of initiatives that must be considered by countries developing pharmaceutical regulations. Some examples of these initiatives follow.

TRIPS Agreement. The TRIPS Agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights) of the World Trade Organization (WTO) has greatly affected international pharmaceutical regulation. TRIPS is an attempt to reduce gaps in the way intellectual property rights are protected around the world and to bring them under common international rules; however, the implications of the agreement's provision on patents caused concerns in developing countries. In response to those concerns, at the Doha Conference in 2001, WTO members adopted a special affirmation—known as the Doha Declaration—on issues related to TRIPS and public health. The declaration affirms that the TRIPS Agreement should be implemented in ways that protect public health and promote access to medicines. Chapter 3 on intellectual property and access to medicines goes into more detail on these issues.

Driven by the increase of global trade in pharmaceutical products and the subsequent complexity of technical regulations related to medicine safety and quality, several initiatives have been established to promote the harmonization of international pharmaceutical guidelines and regulations

by intergovernmental organizations at regional and inter-regional levels.

International Conference on Drug Regulatory Authorities. Organized by WHO, the International Conference on Drug Regulatory Authorities (ICDRA) provides officials from the drug regulatory authorities from all WHO member states with a forum to work on strengthening cooperation and collaboration. Held since 1980, the annual conferences promote the exchange of information

and provide a platform to develop international consensus on pharmaceutical regulation. The conferences are a unique forum that assemble all drug regulatory authorities, regardless of their organizations' stage of development. The ICDRA has been instrumental in guiding regulatory authorities on how the harmonization of regulation can improve the safety, efficacy, and quality of medicines.

International Conference on Harmonisation. The International Conference on Harmonisation of Technical

Country Study 6-1 The evolution of pharmaceutical legislation

Venezuela's first medicine-related law was issued in 1883 as the Ordinance of the Council of Physicians on Secret Medicines and Patents. Pharmaceutical laws have been revised regularly; a significant number of pharmaceutical laws were adopted over the course of the twentieth century. The law that established the medicine registration system—the Law on the Exercise of the Pharmacy—was passed in 1928, before the Ministry of Health was set up in 1936. The National Institute of Hygiene was established in 1938 to serve as the nation's national regulatory agency. Over the years, new rules and organizations have been created to expand the scope of regulation and to add capacity for executing the laws. The section on pharmacological advice, the Laboratory for Pharmacological Analysis, and the Center for Pharmacological Surveillance were established in 1944, 1946, and 1962, respectively. Rules for good manufacturing practices (GMP) were drawn up in 1990. A pharmaceutical law was approved in 2000 that addressed certain concepts for the first time, such as generic and essential medicines.

Tunisia first introduced pharmaceutical regulation in 1942, in the form of a decree on medical and pharmaceutical promotion and medicine control. All finished pharmaceutical products, whether manufactured in Tunisia or imported, must undergo a technical committee review and obtain a certificate of approval from the Ministry of Health before they may be placed on the market. Registration is also required for homeopathic drugs, and some herbal medicines are registered with the status of allopathic medicines. Key legislation includes the 1961 Law on Inspection of Pharmacies and Manufacturers, the 1969 Poisonous Drug Law, and the 1985 Law on Production of Drugs for Human Use. Between 1985 and 1991, several legal texts were promulgated concerning GMP, clinical trials, medical and scientific information, procedures to obtain licensing of manufacturing and registration. New organizations

were also created by law, for example the Pharmacy and Medicines Directorate in 1981, the National Pharmacovigilance Center in 1984, and the National Medicines Control Laboratory in 1990.

In the **Netherlands**, the legal basis for licensing of pharmaceutical manufacturing and distribution was established in 1956. The Medicines Act of 1958 thereafter regulated the admission of medicines to the Dutch market through the Medicines Evaluation Board. But the board started to operate only after 1963, triggered by the thalidomide disaster of 1961. European pharmaceutical regulation is now playing a growing role. In 1995, the European Medicines Evaluation Agency was founded to coordinate the tasks of the drug regulatory authorities of European Union member states. Certain aspects of the Netherlands' pharmaceutical regulation now follow European Union rules. For example, GMP inspection is based on the 1983 European Union guidelines for GMP. Since January 1, 1995, a European procedure for registration has operated in the Netherlands. Now two types of trade licenses exist: a European license and a national license. Products with a European license may be sold throughout the European Union, while the national licenses are valid only for the country in which the license was issued by means of the national registration procedure.

Estonia's drug regulatory framework began to take shape only over the two decades since the country gained independence. However, the pace of regulatory development has been rapid. The Licensing Board of Pharmaceutical Activities and the Center of Medicines were both created in 1991. Registration and licensing were introduced that year. In 1993, the State Agency of Medicines was created to become the Drug Regulatory Authority. The main legislation—the Medicinal Products Act—came into force in 1996.

Source: Ratanawijitrasin and Wondemagegnehu 2002.

Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities and experts from the pharmaceutical industry of Europe, the United States, and Japan to discuss scientific and technical aspects of product registration. The purpose is to promote harmonization in the application of technical guidelines and requirements for new product registration in order to reduce the duplication of and facilitate the evaluation of testing carried out during the research and development of new medicines. Harmonization conserves resources and increases the availability of new

medicines, while maintaining regulatory obligations to safeguard the products. Although intended for new products, ICH guidelines are also being used to register existing products. The guidelines, formally produced by and for ICH member countries, reflect the technical capabilities of their well-developed regulatory agencies and pharmaceutical industries. Thus, other countries should consider their local situations before trying to apply ICH guidelines. However, the ICH guidelines do end up affecting all countries, particularly as they relate to the quality specifications of medicinal products, including generic medicines, the

Country Study 6-2 Harmonization efforts in the Americas

Although subregional harmonization activities have been under way in a number of countries in the Americas (for example, Mercosur, the Andean Community, NAFTA), no overarching mechanism existed for exchanging information and promoting harmonization in the Americas.

In 1999, a hemispheric forum was established, with the Pan American Health Organization (PAHO) as its secretariat, to communicate about pharmaceutical regulation among the different subregions. The resulting organization, known as the Pan American Network for Drug Regulatory Harmonization (PANDRH), has a steering committee that represents the drug regulators of subregional groups active in the pharmaceutical regulatory harmonization process and formulates recommendations on how to promote coordination among the countries. PANDRH includes all representatives involved in addressing the problems connected with pharmaceuticals: regulatory authorities, industry (domestic and multinational), consumers, and professional associations.

In addition, PANDRH has formed a number of working groups to address issues of importance to pharmaceutical regulations including good manufacturing practices, bioequivalence, good clinical practices, drug counterfeiting, pharmacopoeias, and external quality control. Examples of working group activities include harmonizing good manufacturing practices guidelines for inspectors and making the guidelines easily available on the PANDRH website (http://new.paho.org/hq/index.php?option=com_content&task=view&id=1054&Itemid=513); developing specific criteria to prioritize necessary bioequivalence studies; and developing inspection guidelines for audits on good clinical practices, including establishing legal penalties for noncompliance.

The PANDRH steering committee adopted statutes in 2009, which are available on the website.

As PANDRH secretariat, PAHO supports the member countries with—

- Information on pharmaceutical legislation
- Collection and dissemination of documents, experiences, and procedures on drug regulatory harmonization in each country and subregion
- Research to document compliance with existing harmonization agreements
- Definition of the analytical methodology for addressing common problems
- Exchange of information among the harmonization efforts of the different integration processes

Subregional and technical meetings are held often, and PAHO convenes periodic conferences that bring together all the groups to share information and advance harmonization efforts. The Pan American Conference is a meeting open to all interested stakeholders, including consumers, industry representatives, and nongovernmental organizations. Providing an open forum helps ensure the successful adoption and implementation of harmonized outcomes.

One of the major issues of concern to PANDRH members is the recognition that serious limitations exist in some subregions, such as Central America, where no legal framework exists to authorize and operationalize the commitments made by technical groups; therefore, PANDRH takes the particular needs of each subregional bloc and the different degrees of development of their constituent countries into account to implement the subregional agreements. This specificity means that the agreements must be implemented gradually.

Sources: PAHO 2005; PANDRH Steering Committee 2009.

requirements for which vary considerably across countries (Gray 2004). WHO, with its observer status on the ICH steering committee, is expected to act as a link between ICH and non-ICH countries (through the ICDRA) and to disseminate information to non-ICH countries. The ICH has also established a Global Cooperation Group that promotes ICH guidelines by acting as an information resource for nonmembers.

Country Study 6-2 discusses regulatory harmonization efforts in the Americas.

Pharmacopoeias. Pharmacopoeias are documents that outline technical information, manufacturing and testing procedures, and standards for active pharmaceutical substances and products. Some countries, such as Germany and Thailand, also have pharmacopoeias specifically for herbal products. A pharmacopoeia is usually recognized as part of a country's national pharmaceutical laws; therefore, the standards and procedures are legally enforceable. WHO has also developed an international pharmacopoeia that, unlike other pharmacopoeias, has no legal status, but is meant as a reference for member countries that may adapt it and incorporate it into their national legislation. Because of the extensive resources required to produce and maintain these complex documents, most countries do not have national pharmacopoeias and rely on one or more internationally recognized pharmacopoeias, such as those from the United States, the European Union, Japan, or WHO. The organizations that publish pharmacopoeias, pressured by the need to facilitate international trade, are actively working to harmonize their requirements.

Drafting and revising pharmaceutical legislation and regulations

Regulatory authorities are continually faced with new issues—such as globalization and extension of free trade—while increased responsibilities from market expansion and the sophistication and new categories of products place heavy demands on regulatory systems. The development of cutting-edge technologies and health care techniques and the extensive use of the Internet as a source of information and commerce impose further complex challenges.

As a first step before drafting any new law, it is important to inventory the laws and regulations already in force. Even if no general drug law exists, pieces of legislation are likely to touch on the field—for example, laws on narcotics and the licensing and responsibilities of pharmacists. An out-of-date general drug law may exist that should be replaced rather than merely amended. Determining the extent to which existing laws and regulations contribute to attaining the national policy objectives is essential. Because concepts of pharmaceutical policy are modern, legislation more than twenty years old may not be relevant; starting over may be simpler.

The second step is for drafters and experts to meet to decide what type of legislative instrument is required. The most straightforward model is likely to be a comprehensive law that deals in outline with all the relevant issues, each main section taking up a particular matter. Sections can then be implemented one at a time, through the passage of regulations.

In countries with a long history of regulation, laws on pharmacists and the registration of medicines as well as regulations on prices and costs are likely to be separate, because they came into being at different times. In starting afresh, however, and particularly if the laws on these matters are outdated or incomplete, it may be easier to pull together all relevant elements into a single law.

Ideally, the task of writing or revising the law should be entrusted to a group of legal and health experts who are familiar with all the issues, but not all countries can assemble such a group. Rather than solving the problem by copying laws from abroad, countries with limited expertise can obtain assistance from international and bilateral agencies to draft new pharmaceutical legislation that meets the country's own needs. International and regional meetings of drug regulatory authorities (for example, ICDRA) also provide opportunities for learning how to approach the problem and identifying expert colleagues who can be called on for advice. In addition, WHO has a number of publications that can assist countries in developing national medicine policies (available at http://apps.who.int/medicinedocs/en/cl/CL1.1.1.1.2/clmd,50.html#hlCL1_1_1_2).

At all stages of the process, it is important to discuss early drafts of the law with all interested parties, including the health professions, trade and industry groups, other concerned government departments (such as those handling commerce and education), and consumer groups. The greater the consensus, the greater is the chance that a law will be passed and will work in practice. Sometimes, countries react to a crisis by rushing through the enactment of a new law without putting it through a consensual process or carefully evaluating its effect on other sectors. However, this attempt to respond quickly may backfire if the law is not carefully thought through.

When the law is approved, regulations are developed to guide the implementation of the law. Regulations can be modified more easily than laws as the local situation evolves. When a regulation is revised, it is important to research and take into account what other laws will be affected by the revision. Declaring that a revision nullifies all previous laws and regulations in conflict, without making sure what those previous laws cover, can result in confusion. It is easier to track revisions when a country's laws are well codified, such as in the *U.S. Code of Federal Regulations*. Following the adoption of regulations, guidance documents may be developed to provide more flexible and detailed information on how to comply with regulations.

Box 6-1 Elements of a comprehensive drug law

A. General provisions

1. Title*
2. Purposes*
3. Territorial extent
4. Application of other laws
5. Definitions*

B. Control of availability and marketing

1. Drug registration*
2. National essential medicines list/national formulary
3. Scheduling prescription, and dispensing authority*
4. Labeling*
5. Generic labeling, manufacturing, and substitution
6. Pharmacovigilance
7. Information and advertising*
8. Public education
9. Imposition of fees
10. Price control
11. Special products (herbal medicines, medicines for clinical trials, orphan drugs)

C. Control of supply mechanisms

1. Importation of medicines*
2. Exportation of medicines*

3. Controls, incentives, disincentives for local manufacture
4. Control of distribution, supply, storage, and sale*

D. Drug control administration

1. Organization and function*
2. Appeals against decisions of the drug control authority*

E. Powers of enforcement

1. Prohibition of specified activities*
2. Penalties for each offense based on magnitude and occurrence*
3. Legal procedures for offenses*

F. Powers to make rules and regulations

1. Who has authority*
2. Under which circumstances*

G. Repeals and transitional provisions

1. Repeal of sections of existing laws in conflict with the act
2. Transitional period to implementation*

H. Exemptions from provisions of the law*

* Elements for which model legislation has been developed by WHO.
Sources: Adapted from WHO 1998b, 1999c.

6.2 Basic elements of national pharmaceutical legislation

A well-defined set of elements constitutes the initial requirements for a strong and comprehensive national pharmaceutical law. These elements, though basic, are sufficiently wide and varied in their scope to meet most of the objectives of a national pharmaceutical policy. Box 6-1 presents a model for national pharmaceutical legislation, showing the various key elements. This model can be adapted to support the efforts of small national drug regulatory authorities in countries where only one or two professionals are available to deal with pharmaceuticals and related products.

6.3 Key provisions of national pharmaceutical legislation

Because a consumer cannot independently assess the safety, efficacy, or quality of pharmaceuticals, these products are

universally recognized as being different from ordinary items of commerce, such as clothing or household appliances, and therefore in need of handling by specially trained health professionals. These requirements make pharmaceuticals subject to numerous controls at all levels, and legal authority is granted to regulate their manufacture, distribution, marketing, prescribing, labeling, dispensing, and related activities, such as pricing.

An effective national pharmaceutical law is a primary means of ensuring that pharmaceutical policy goals are achieved while the unique character of pharmaceutical products, personnel, and facilities is preserved. The law may specify what products can legally be imported—for example, those included on the national medicines list and possessing a WHO-type certificate of quality—and which individuals are legally qualified to prescribe and dispense them, thus promoting certain national pharmaceutical policies.

Likewise, control of the manufacture, storage, distribution, and sale of pharmaceutical products enables a government

to better ensure compliance with a national policy of having essential medicines of appropriate quality, safety, and efficacy available for their intended purposes. The processes of licensing and registration can grant authorization only to those personnel, products, and facilities that conform to the national pharmaceutical law. For example, counterfeit or dangerous medicines can be taken off the market, and sanctions can be taken against those responsible for introducing them illegally.

In addition, countries that host clinical trials to test new medicines should incorporate regulations on how the studies should be conducted, including an application process that explains the purpose and protocol of the intended research and the creation of an ethics committee to approve and monitor any study protocol that includes human participants. For countries needing assistance in this area, WHO publishes guidelines on good clinical practices (WHO 2005b).

The promulgation of regulations, the collection of licensing and registration fees, and the enforcement of the national law and its regulations are legally delegated to an agency—usually called the national drug regulatory authority—headed by a commissioner or director who is responsible to a cabinet-level person, such as the minister of health. For example, in the United States, the basic national pharmaceutical law is called the Federal Food, Drug, and Cosmetic Act, which is enforced by the Food and Drug Administration. For controlled substances, additional restrictions are imposed by the Drug Enforcement Administration. In the United States, wholesale distributors, pharmacy practice, and medical practice are regulated by individual states.

Defining the roles of various parties

Because so many parties are involved with medicines, the laws need to clearly state the roles, responsibilities, and rights of each, ranging from practitioners, auxiliaries, nurses, and pharmacists to importers, manufacturers, and distributors. Countries approach prescribing and dispensing differently, depending on their circumstances; for example, in Canada, a physician must be the medicine prescriber, but in areas where physicians are scarce, legal authority may be granted to nurses or other health practitioners to prescribe essential medicines. The legislation should establish the qualifications required for those handling medicines, or it must state who has the authority to set these standards by passing appropriate regulations (for example, a government minister).

Licensing, inspection, and quality control

The law should create mechanisms to ensure that relevant parties are licensed and inspected so the community can have confidence in them. Doctors and nurses may be covered by other laws, but the medicine law needs to ensure that

the people who import, distribute, and sell medicines are properly qualified, approved, registered, and inspected.

Pharmaceuticals themselves require a special form of inspection. An inspector visiting a pharmacy or warehouse may have reason to suspect that medicines are not of sufficient quality or in good condition: they may be damp, dirty, or disintegrating. More often, samples need to be obtained for testing in the quality-control laboratory, an essential part of the inspection system.

Some countries have their own quality-control laboratories, either specifically for medicines or shared with other commodities (such as foods). A number of countries use regional laboratories, such as the ones serving sub-Saharan Africa or the Caribbean. Whatever the structure, the pharmaceutical law needs to designate a quality-control laboratory that has the capacity and equipment to do the job.

Countries that have pharmaceutical manufacturing operations should enforce good manufacturing practices (GMP), which is a system to ensure that products are consistently produced and controlled according to quality standards. GMP covers all aspects of production from the starting materials, premises, equipment, and quality testing to the training and personal hygiene of staff. WHO has established detailed guidelines for good manufacturing practice, and many countries have formulated their own requirements based on WHO's GMP. Other regions, such as the Association of Southeast Asian Nations and the European Union, have harmonized their GMP requirements.

Although important, GMP monitoring sometimes receives more resources than the inspection of distribution channels; however, the consumer's interest is not served by manufacturing a product under GMP but then storing and distributing it under adverse conditions. Inspection of distribution channels, including the importation of pharmaceuticals, should also be emphasized, particularly in countries where the distribution system has several intermediate levels or the climate is unfavorable. WHO has produced guidelines relating to good storage practices for pharmaceuticals (WHO 2003a).

Chapter 19 has more information on quality-control and inspection procedures.

Pharmacovigilance

The law should also provide a basis for a pharmacovigilance (that is, postmarketing surveillance) system to report problems with adverse reactions and product quality. *Pharmacovigilance* is defined by WHO (2002a) as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.”

Pharmacovigilance is an overarching concept that encompasses any system used to monitor medicine safety, use,

and efficacy. For example, adverse drug reaction monitoring as part of a product's postmarketing surveillance contributes to the assessment of benefit, effectiveness, and risk of medicines. A pharmacovigilance system is difficult—if not impossible—to implement in an unregulated market that allows the importation and sale of pharmaceuticals

through informal channels or the sale of powerful medicines without prescription. Drug regulatory agencies should have access to information from the WHO Programme for International Drug Monitoring (http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Joining_WHOProgrammeForInternationalDrugMonitoring.pdf),

Box 6-2 Adverse drug reaction monitoring

An adverse drug reaction (ADR) is a harmful and unexpected reaction to a drug taken at a normal dosage. The research done on medicines before they are allowed on the market is incomplete; generally fewer than 5,000 people have been exposed to the medicine in premarket tests, an insufficient number to detect less common ADRs. In addition, information on chronic toxicity and reactions in special groups, such as pregnant women and children, is often unavailable from this premarket research, because these groups are usually not included as subjects in clinical trials. Postmarketing surveillance, therefore, allows for the detection of rarer, but possibly critical ADRs. In addition, postmarketing monitoring may detect counterfeit or substandard products. Often, a country's national drug regulatory authority is responsible for ADR monitoring and reporting.

To facilitate information gathering, the drug regulatory authority should provide case report forms to health providers on adverse drug reactions. The completed case report form is then sent to the national or regional ADR center or to the manufacturer of the product. These forms vary by locale, but should include the following minimum information.

Patient information—

- Patient identifier
- Age at time of event or date of birth
- Gender
- Weight

Adverse event or product problem—

- Description of event or problem
- Date of event
- Date of report
- Relevant tests/laboratory data
- Other relevant patient information/history
- Outcomes attributed to adverse event

Suspected medication(s)—

- Name (international nonproprietary name and brand name)

- Dose, frequency, and route
- Therapy date
- Diagnosis for use
- Event abated after use stopped or dose reduced
- Batch number
- Expiration date
- Event reappeared after reintroduction of the treatment
- Concomitant medical products and therapy dates

Reporter—

- Name, address, telephone number
- Specialty and occupation

It can take years or even decades before adverse events are linked to the use of particular medicines. For example, several years passed before certain birth defects were associated with thalidomide use by pregnant women; decades passed before aspirin was linked to gastrointestinal problems. In some cases, medicines are withdrawn from the market, as was the case with bromfenac, terfenadine, and encainide after they were connected to serious health outcomes. In other cases, labeling is changed to include the new information on effects, contraindications, or dosage as a result of information received through postmarketing surveillance.

Clearly, the usefulness of a postmarketing surveillance program depends on cooperation from health professionals. All health care providers, including physicians, pharmacists, nurses, dentists, and others, should report ADRs as part of their professional responsibility. Even when some doubt exists about the relationship between the product and the ADR, all suspected ADRs, especially related to new medicines, should be reported as soon as possible. Many countries provide an easy system for reporting ADRs to their drug regulatory authorities, such as a dedicated phone line as provided in Ghana and a special reporting website as in Brazil.

Source: WHO 2002c.

which provides a clearinghouse for the millions of adverse drug reaction reports received from almost 100 countries. International pharmacovigilance activities have had a notable effect on international drug regulation. Box 6-2 describes the elements that comprise an adverse drug reaction program, and Chapter 35 has more information on implementing a pharmacovigilance program.

Advertising and promotion

Although many countries have rules to ensure that advertising is not misleading, these rules are generally not sufficient to cover pharmaceuticals. With consumer products, a certain degree of exaggeration is often tolerated as the normal practice of the marketplace. But for medicines that have the capacity to kill or cure, and with claims that people cannot easily verify, it is important that advertising to health professionals and to consumers be objective and reliable; misleading and extravagant pharmaceutical advertising claims may pose significant risks to the public.

For these reasons, most laws on pharmaceuticals now include a clause empowering regulation on advertising. In many countries, it is illegal to advertise to consumers medicines intended to be prescribed by health professionals. However, direct promotion of pharmaceutical products through the Internet is practically impossible to control; therefore, the national regulatory agency should educate consumers on identifying reliable sources of information, preferably in collaboration with national consumer and professional organizations. All advertising and labeling must be consistent with the information verified when the pharmaceutical product was registered or approved for marketing, with modifications required by the regulatory authority on the basis of postmarketing experience.

Useful guides to the principles that should underlie honest pharmaceutical promotion have been issued by WHO and separately by manufacturers (WHO 1988, 1999b).

Sanctions

Because constant vigilance is needed if the public is to be protected, pharmaceutical laws must be properly enforced with appropriate penalties for violators. There is no use establishing that medicine quality is poor, a warehouse is rat infested or damp upon inspection, or an advertisement is untruthful unless something is done about it. The drug regulatory agency must use its authority to impose appropriate penalties when necessary: sanctions may be penal (fines, imprisonment, or both) or simply corrective (banning the drug, closing down the warehouse). Sometimes a party has contravened the law so seriously that the appropriate sanction is determined to be loss of license to prescribe, manufacture, import, or distribute. On occasion, all of the penalties may be imposed.

To be effective, the drug regulatory authority must be able to apply sanctions on a timely basis, so it must have either the legal staff to ensure compliance or the necessary links with the relevant government department charged with enforcement. Therefore, the law governing pharmaceutical products must give legal authority to the appropriate personnel to carry out any necessary enforcement activities.

In addition, because the pharmaceutical sector is vulnerable to corruption, a country should not only include an anticorruption mechanism in its regulatory framework, but also have sanctions in place for bribery, fraud, collusion, and other dishonest acts (WHO/PSM 2006). Many countries have specific laws that address corruption in the public sector or provisions in their procurement regulations to ensure transparency and provide sanctions against, for example, bribery.

6.4 Medicine registration, licensing, and marketing authorization

The licensing and inspection of manufacturers and importers, although important, do not provide assurance about the products. Many countries have evolved systems of drug registration to ensure that individual products approved for sale meet the following criteria—

Efficacy: The medicine should be shown to be effective for the indications claimed. However, note that no product is ever 100 percent effective for all users. In practice, efficacy means that in a majority of cases the product meets its therapeutic claim.

Safety: The medicine should not present risks that are disproportionate to its benefits. Some patients may suffer severe reactions even to medicines shown to be safe in clinical studies. However, in the great majority of cases, adverse effects are minor or very infrequent.

Quality: The medicine should be well made, as specified in the official pharmacopoeia chosen as a standard. If not listed in an official pharmacopoeia, the product's manufacturing should comply with the quality documentation submitted by the applicant that demonstrates its safety and efficacy.

Clinical use information: All the clinical information needed to use the medicine properly, including indications, doses, precautions, and adverse effects, should be provided as part of the packaging, in language understandable to the health professional or patient, as appropriate.

Medicine registration, also referred to as licensing or marketing authorization, is often a major element in national pharmaceutical law. In its fully developed form, however, it is costly and labor intensive. Establishing a drug registration system is generally not justified until a country has a

Box 6-3
Stages in the evolution of a medicine registration system

Stage 1: Notification procedure. Standard information is obtained on all pharmaceutical products currently marketed in the country and entered into a register. No judgment is made at this time regarding the appropriateness of the drugs for sale in the country.

Stage 2: Basic authorization procedure. Products listed in the register are provisionally authorized to remain on sale. All other drugs that are to be sold require a license, which is issued after an appropriate assessment of the efficacy, safety, and quality and a review of truth and completeness of packaging and labeling information.

Stage 3: Full registration or licensing procedure. Full evaluation of individual products is conducted by examining detailed data submitted by the manufacturer and obtained from the literature to assess their quality, safety, and efficacy.

Stage 4: Reevaluation of older drugs. All older pharmaceutical products on the market are systematically reassessed for compliance with the standards.

significant volume of private-sector pharmaceutical sales. The primary concern of many resource-limited countries is ensuring a reliable flow of essential generic drugs from reputable suppliers into the public health system.

As a country's economic development proceeds and more resources become available, priorities may change. The private sector may become more active, and local and multinational firms may begin actively promoting their new products to prescribers and even to the public. At this point the need for a medicine registration system arises.

As proposed in the WHO (1999c) guidelines for small drug regulatory authorities, a medicine registration system can best be developed in stages, starting with an inventory of all pharmaceutical products on the market, followed by a provisional authorization that allows products to continue to be sold until they complete the full registration procedure as shown in Box 6-3. Country Study 6-3 shows how Namibia maximized its resources by streamlining its medicine registration system.

In stage 1, the information requested initially may be simply the international nonproprietary name; product trade name, if any; name of the manufacturer; and country of origin. Later, this can be expanded to include composition, including inactive ingredients; pharmacological action; therapeutic classification; and claims made in the package

insert. Having a complete register of what is on sale in the marketplace allows the regulatory agency to evaluate information from other countries or from WHO about problems with a particular medicine (for example, toxicity, contamination, evidence of inactivity), to determine whether the product is on sale in their country, and what actions might be taken.

Stage 2 requires assessment for new pharmaceutical products. Because this procedure is costly and time-consuming, countries can rely on decisions made in other countries with well-developed regulatory agencies, such as those that are members of the ICH. Is the drug approved for sale in its home country? If so, what claims have been made for it? Does it carry a WHO-type certificate indicating that it is manufactured under satisfactory conditions? The firm wishing to import the product must provide documented answers to these questions. Regulatory authorities may consult other countries directly before deciding to accept or reject a product. WHO and other bodies hold international and regional meetings of regulatory authorities from different countries, which helps create trust across borders and facilitates informal work sharing. Approval of locally manufactured pharmaceuticals requires inspection of the manufacturing premises and staff.

The task of full registration described in stage 3 should never be taken up lightly—even a large regulatory agency can be overwhelmed by the vast amount of material that needs to be examined. Some groups of countries handle assessment jointly; others look at where else in the world the medicine is licensed, and under what conditions. Countries that have the resources to handle registration and licensing independently can often obtain technical advice and practical help from WHO and support from other countries with well-developed regulatory agencies.

Stage 4, the reevaluation of older products on the market, is the final stage in the development of a registration system and is very ambitious. Few industrialized countries have yet managed to complete it.

If a medicine is intended to be generically equivalent to another already on the market, regulations must stipulate the evidence needed to support their equivalence (see Box 6-4). WHO has a resource for countries without a fully functioning system for premarket evaluation and market authorization that wish to assess and authorize multi-source (generic) pharmaceutical products (WHO 1998b). WHO also makes available findings from assessment reports generated as part of its program to prequalify medicines for HIV/AIDS, tuberculosis, and malaria, including information based on product data showing compliance with international standards for quality, safety, and efficacy, bioequivalence (for generic products), and findings resulting from inspections of production sites according to GMP standards (see <http://mednet3.who.int/prequal/>). The WHO prequalification process should be useful to

Country Study 6-3 Revising registration procedures in Namibia

In its first fifteen years of independence, Namibia developed very comprehensive pharmaceutical regulatory procedures, considering its small population and limited resources. Unfortunately, human resources capacity did not keep pace with administrative requirements, and the number of medicine registration applications quickly created a huge backlog of about 1,000 medicines awaiting marketing approval, including antiretroviral (ARV) medicines. At that time, forty-nine ARVs were on the market, but the backlog prevented access to valuable fixed-dose combinations and pediatric products. One estimate showed that at the current capacity, it would take eighteen years to review all outstanding applications.

The Rational Pharmaceutical Management (RPM) Plus Program worked with the government on interventions to streamline the registration process. Key was a policy change allowing the Medicines Control Council (MCC) to give priority to ARVs for registration and create a proxy evaluation process to quickly accept prod-

ucts already registered in International Conference on Harmonisation countries or South Africa; for example, the new policy permits the MCC to accept certain quality requirements that have already been approved by recognized authorities, such as through WHO's prequalification program. Other interventions included training nonprofessional staff to take on some application processing responsibilities and creating a drug registration database.

Within a year after RPM Plus's intervention began, 1,392 applications for new medicines were evaluated. Of those, fourteen ARVs and twenty-four generic ARVs were reviewed and approved (which increased the number of ARVs on the market by 75 percent). The fourteen approvals included much-needed pediatric dosage forms and fixed-dose combinations; the addition of generic products helps reduce prices.

Source: Pereko and Nwokike 2006.

Box 6-4 Interchangeability

New multisource (generic) pharmaceutical products must be of good quality and at least as safe and efficacious as existing products. The need for interchangeability arises when a patient changes from one brand to another, for example, when—

- Physicians prescribe by generic name
- Generic substitution is permitted by national legislation
- The same brand is not always available, for example, in remote areas of the country
- Patients in hospitals are given whatever brand the hospital has in stock, and sometimes different brands on different occasions
- Patients receive a different brand after discharge from the hospital

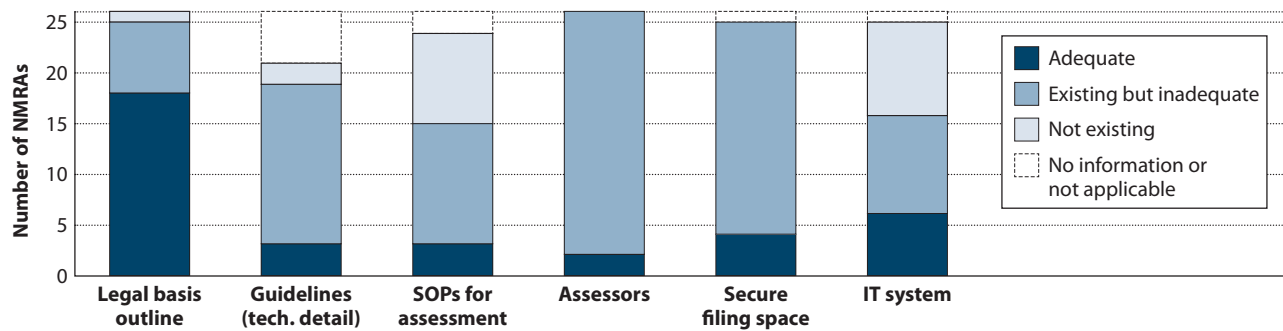
A number of features are important to interchangeability, although the science behind demonstrating interchangeability is still evolving: compliance with appropriate

quality standards and at least compliance with relevant pharmacopoeial standards; stability; possible differences in sensitizing potential caused by the use of different excipients; therapeutic equivalence in terms of, as appropriate, bioequivalence, pharmacodynamic studies, clinical studies, or in vitro dissolution rate; and product information and labeling.

By their nature, different brands of modified (sustained-, continuous-, prolonged-, slow-) release products are more likely not to be equivalent than are different brands of immediate, conventional-release products. Some drug regulatory agencies take the view that such products should never be considered interchangeable, while others define a series of studies that should be conducted, including in some circumstances comparative clinical trials. For delayed-release products, such as enteric-coated tablets, interchangeability is more easily demonstrated.

Source: WHO 1998b.

Figure 6-1 Resources for medicine registration in twenty-six African countries



NMRAs = national medicine regulatory authorities; SOPs = standard operating procedures; IT = information technology.

Source: Adapted from WHO 2010b.

developing-country regulatory authorities that do not have sufficient capacity to fully assess products and determine their acceptability before licensing.

The registration systems of many African countries are still lagging. For example, in twenty-six countries surveyed, the technical standard of evaluations, if they existed, were not in line with WHO standards; only 11 percent had adequate standard operating procedures for assessment, 85 percent did not have enough space to store data securely, and only one-quarter of the countries had functioning computerized registration systems (WHO 2010b) (see Figure 6-1).

Classifying pharmaceuticals for dispensing

As part of the marketing authorization process, the national drug regulatory agency is also responsible for classifying each pharmaceutical product in terms of how it is dispensed and sold. For example, prescription-only medicines require a directive from an authorized health practitioner; pharmacist-only medicines are available without prescription, but only under a pharmacist's supervision; and over-the-counter medicines are available without a prescription in retail outlets besides the pharmacy, such as a grocery or licensed drug seller. This classification affects the product's availability and appropriate use. Factors to consider in the classification include—

- The safety of the active ingredient
- The need for professional counsel before use
- The nature of the ailment or symptoms the medicine is intended to treat
- The risk/benefit ratio (TGA 2003)

Consideration should also be given to the restrictions for prescribing and dispensing controlled drugs as provided in the international drug control treaties, namely the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances. The list of narcotic

and psychotropic drugs is available from the International Narcotics Control Board (<http://www.incb.org>).

Regulating traditional and herbal medicines

As discussed in Chapter 5, countries are increasingly recognizing the large role that traditional and complementary medicine plays in their health care systems. An important challenge is the evaluation and assurance of the quality, safety, and efficacy of herbal and traditional medicines. Since the earliest days of humankind, herbal medicines have been applied in health care throughout the world. Many are still widely used and have become important in international trade. Significant quantities of herbal products are now imported by countries in the European Union, North America, and Asia. However, the use and production of herbal products remains largely unregulated, and their safety and therapeutic value cannot always be guaranteed.

Recognition of the clinical, pharmaceutical, and economic value of herbal medicines is growing, although the level of official recognition through legislation varies widely among countries. WHO published a reference on the national experiences of fifty-two countries in formulating policies on traditional and herbal medicinal products and in introducing measures for their registration and regulation (WHO 1998c). WHO also published a summary of the legal status of traditional and complementary medicines in 141 countries (WHO 2005c) and guidelines on how to develop national policies on the safety, efficacy, and quality of herbal medicines (WHO 1998a).

6.5 Controlling alternative and informal distribution channels

In some countries, unregulated, informal, or even illegal distribution (including sales in marketplaces and on streets) and smuggling of medicines are widespread. Another major

problem is that medicines may be traded through several intermediaries and free-trade zones and are sometimes repackaged and relabeled to hide their true source or identity, leading to the circulation of substandard and counterfeit medicines.

As the volume of expensive medicines such as for HIV/AIDS and malaria increases in formal distribution channels, there will be an increase in leakage of these medicines to informal channels. A WHO study of regulations in ten countries (Ratanawijitrasin and Wondemagegnehu 2002) showed that pharmaceuticals distributed through the informal sector received little regulatory attention from governments compared with those distributed through the formal sector. Products of substandard quality and incorrect information—especially exaggeration about efficacy—are often found in the informal sector.

It is important for countries to assess the influence of alternative and informal distribution channels on their health care systems. If citizens purchase most of their medicines from informal dealers, they may be getting substandard-quality products, which may adversely affect public health. Medicine regulation can be used to promote quality criteria for medicines and health commodities by establishing and enforcing standards for all distribution channels and encouraging the public to be careful about where they buy pharmaceutical products. Chapter 32 discusses how initiatives can improve the quality of products and services from private-sector drug sellers. Country Study 6-4 describes how

the government in the Lao People's Democratic Republic (P.D.R.) has instituted regulations to improve the quality of private pharmacies.

Another challenge to drug regulators that has emerged in recent years is the widespread use of the Internet to sell uncontrolled pharmaceuticals across national borders (WHO 2003b). Regulation and enforcement can deter illegal practices, although it requires cooperation among national agencies such as those handling drug regulations, customs, and the postal service. Because of the transnational nature of e-commerce, international cooperation in its control is also needed.

6.6 Substandard and counterfeit medicines

Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications and consequently may be ineffective, dangerous to the patient, or both. Substandard products may occur as a result of negligence, human error, insufficient human and financial resources, or counterfeiting.

Counterfeit medicines are considered a subset of substandard medicines, but the difference is that they are deliberately and fraudulently mislabeled regarding their identity or source. Counterfeiting can apply to both branded and generic products, and counterfeit medicines may include products with the correct ingredients but fake packaging,

Country Study 6-4 Regulatory interventions in Lao P.D.R.

In Lao P.D.R., private pharmacies make up the majority of the retail market for medicines. However, little or no control of private pharmacies existed until 1996, when such regulation was incorporated into the National Drug Policy. District pharmacists became responsible for inspecting and monitoring private pharmacies, and a special unit was created at the provincial level to oversee the regulations. Inspectors made sure that the pharmacies had up-to-date regulatory documents. In addition, the central drug regulatory authority instituted a number of policies to improve the quality assurance system in the country. These included the development of a good manufacturing practices regulation with associated training, improvements in the medicine registration system, and the institution of fines and sanctions to enforce the new regulations.

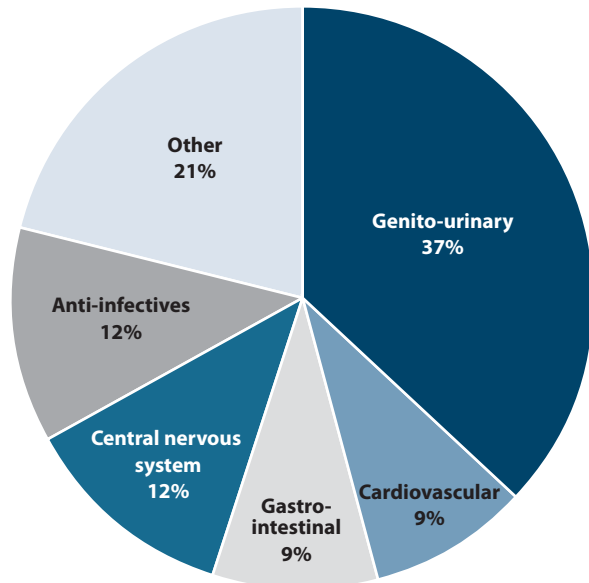
In 1997, a baseline assessment was conducted in 115 of 214 licensed private pharmacies in Savannakhet province before the new regulations had fully taken hold.

A follow-up study in 1999 used the same indicators to assess the effect of the new policies and activities on private pharmacy services. The results showed significant improvement in almost all indicator values, including the organization in the pharmacy; availability of essential medicines and essential materials for dispensing, such as a hygienic counter; and information given to the customers. Analysis of samples from the 115 pharmacies showed a decrease in the proportion of substandard medicines—from 46 percent in 1997 to 22 percent in 1999—still high, but substantially better.

Before the regulatory interventions, the quality of pharmaceutical service was low in Savannakhet province. The development of a regulatory framework with regular inspections and enforcement through sanctions was not only possible to initiate in a resource-limited country, but also appeared to be an important catalyst for better quality medicines and pharmacy practices.

Sources: Stenson et al. 2001; Syhakhang et al. 2001.

Figure 6-2 Reports of counterfeit medicines by therapeutic class received in 2007



Total number of cases: 1,513. One case reflects at least one production lot (e.g., thousands of tablets, capsules, or other forms).

Data from the Pharmaceutical Security Institute (<http://www.psi-inc.org>).

with the wrong ingredients, without active ingredients, or with insufficient active ingredients.

In wealthier countries, the most frequently counterfeited medicines are new, expensive lifestyle medicines. In developing countries, the most counterfeited medicines are those used to treat life-threatening conditions such as malaria, tuberculosis, and HIV/AIDS. Figure 6-2 gives the number of reports of counterfeit medicines, by therapeutic class, submitted in 2007 and shows that the highest percentage reported concerned genito-urinary medicines.

Trade in these medicines is more prevalent in countries with weak pharmaceutical regulatory control and enforcement, scarce or erratic supply of basic medicines, unregulated markets, and unaffordable prices. Governments need to develop strategies and put appropriate legislation and sanctions into place to reduce corruption and criminal activity. As in the case of e-commerce, enforcement of these laws requires cooperation among regulatory authorities, police, customs services, and the judiciary to control more effectively the pharmaceutical market.

6.7 Establishing effective administrative control

In many countries, medicine legislation and regulation are not regularly updated or are imported from other countries and do not reflect national realities. Countries can draw

guidance from the experiences of others, but problems have arisen when overly complex provisions were adopted. Legislation and administrative practices must be attuned to available resources, and every opportunity must be taken to understand and use the information provided by regulatory authorities in other countries (WHO 1990). The example of approving microbicides to control HIV infection shows the regulatory difficulties faced by resource-constrained countries (Box 6-5).

Required resources

To perform effectively, national regulatory authorities must have the necessary political support, legal power, human and financial resources, and independence in decision making. They also must have strong public support and proper management. Where national regulatory authorities have a high profile within the government, they are organized as a commission, board, statutory authority, or department, with the legal power from government to acquire and use resources, including hiring qualified full-time staff at a salary scale that discourages corruption and conflicts of interest.

Ideally, one central, autonomous agency should be accountable for the overall effectiveness of pharmaceutical regulation. In countries whose regulatory functions are split among two or more agencies, the fragmentation can lead to duplication of effort, lapses in implementation, inconsistent regulation, and wasted resources. In recent years, several countries (for example, Argentina and Brazil) have successfully established such centralized agencies to regulate food, medicines, and consumer products. However, a survey of twenty-six countries in sub-Saharan Africa showed that most countries' regulatory systems were uneven—with gaps and overlaps in responsibilities spread over several bodies other than the drug regulatory authority, including the ministries of trade and health, pharmaceutical councils, and regional authorities, especially for licensing and inspection (WHO 2010b).

Table 6-1 details the resources required to achieve effective administrative control; at a minimum, these needs include a drug regulatory authority with staff, a team of inspectors to visit warehouses and retailers, and access to a laboratory capable of performing quality-control testing.

Personnel are the key resource for making effective pharmaceutical regulation possible. Because of the technical nature of their work, the law often prescribes that inspectors be pharmacists or have other relevant education and training. Others can be trained to undertake licensing, registration, and enforcement duties. Depending on the size of the country and the degree of pharmaceutical development, the entire staff may consist of only a few individuals. Sometimes contracting out specific duties may be appropriate; however, it is important for the contractor not to have any conflicts of

Box 6-5**Regulatory hurdles in the development of microbicides for HIV/AIDS**

More women than men account for new HIV infections in many parts of the world. In certain places, women's lack of power means they cannot insist on condom use to protect themselves, and even if they have a single partner or husband, they are still at risk. This situation has resulted in much interest in the development of microbicides—a topical medicine used vaginally to prevent HIV transmission—that gives women control of usage.

A major obstacle to the approval of an effective microbicide is the fact that those now in clinical testing are new medicines that have not been on the market yet. Many developing countries do not have the resources or regulatory framework available to perform the testing and review of new medicines themselves, so they rely on product reviews from the United States or Europe to determine acceptability for their countries. However, because microbicides will be marketed primarily in developing countries, developed countries have no incentive to review and license them for their own markets.

To help fill the gaps, the European Parliament approved an initiative for the European Medicines Agency (formerly known as the European Medical Evaluation Agency) to scientifically assess products such as microbicides that are proposed for use primarily in developing countries. The drug regulatory agencies in developing countries would then use the scientific assessments to make decisions about licensing. Other steps that could help overcome these regulatory hurdles would be collaboration between regulatory authorities in developing and industrialized countries to jointly review product profiles and to help resource-limited countries develop the capacity to make drug registration decisions autonomously.

Although results of clinical trials of microbicides for HIV have been mixed, research continues, and the European assessment mechanism is one that could be used with other similar products.

Sources: Coplan, Mitchnick, and Rosenberg 2004; Davis 2009; Fox, Beasley, and Kelland 2010.

interest, such as an ongoing consultancy with a pharmaceutical company that could specifically benefit from the contracting arrangement.

Computer software now greatly simplifies many of the administrative tasks of the regulatory agency. Personnel should have access to the latest scientific and technical information to facilitate their work.

Financing

The law must provide a realistic mechanism for funding regulatory functions. Funds may be provided from general tax income and from charges levied on the manufacturers, importers, and distributors to cover the bulk of the costs of the pharmaceutical control system. The level of charges may be set from year to year, but the nature of the charges can be defined in the law. For example, the law may set lower fees for essential medicines; importers can be required to pay a fee when they submit a new medicine application to the regulatory authority for consideration, a supplementary fee when the license is issued, and an annual fee for as long as the medicine remains on sale; and manufacturers might be required to relicense their products periodically (for example, every five years).

Fees and charges substantially fund the cost of operating the national regulatory agencies in most developed and some developing countries. In Canada, the United Kingdom, and the United States, the agencies recover 70

percent, 100 percent, and about 50 percent, respectively, of their regulation costs (WHO 2003b). Because of their large markets, developed countries tend to charge higher fees than developing countries. In addition, in developing countries, fee revenues are often added to the general treasury rather than being assigned specifically to the drug regulatory agency, which makes it hard to adequately finance regulation. However, regulatory agencies should not be completely dependent on fees to fund all of their activities; they should receive some financial support from their governments to help ensure their independence and ability to carry out basic responsibilities. Most of the twenty-six drug regulatory authorities surveyed in Africa get their funding from more than one source (e.g., fees, government, donors); however, none had sufficient or sustainable operating funds (WHO 2010b).

Guiding principles for small national drug regulatory authorities

Regulation is not the only component of pharmaceutical policy, and sometimes in resource-limited settings, it is not even the most pressing one. Nonetheless, the existence of a well-functioning national drug regulatory authority to help ensure medicine quality, safety, and efficacy is the best guarantee that the public is getting the medicines it deserves. A national regulatory authority needs a clear mission statement including goals and objectives to direct its work. Goals

Table 6-1 Resources required for effective administrative control

Resources required	Specific function or purpose
Personnel	<ul style="list-style-type: none"> • Regulatory activities (licensing, registration, and so forth) • Monitoring, inspection, and surveillance • Enforcement
Physical and infrastructure	<ul style="list-style-type: none"> • Office space for regulatory and enforcement personnel • Access to appropriate analytical laboratory resources • Computers, software, sampling equipment, and office equipment • Vehicles for distribution, inspection, and enforcement activities
Technical	<ul style="list-style-type: none"> • Preservice and in-service training • Knowledge of pharmaceutical manufacturing processes, packaging, and so forth • Collation of data • Dissemination of information • Reference library (books, journals, bulletins)
Financial	<ul style="list-style-type: none"> • Capital and recurrent expenditures • Technical programs • Payments for patents and royalties • Payments for consultants • Payments for quality-control samples • Publications (forms, licenses, pharmacopoeia) • Travel for inspection and enforcement activities

Source: Adapted from Jayasuriya 1985.

usually include protecting public health by ensuring the safety, efficacy, and quality of medicines and their appropriate use. Plainly outlined objectives provide a measure to evaluate how well the agency is functioning.

Primary pharmaceutical regulation activities should not be compromised by other nonregulatory tasks with which the national regulatory authority may be charged. If the authority responsible for pharmaceutical regulation has nonregulatory functions, such as manufacturing, procurement, or service delivery, conflicts of interest may occur regarding mandates and resource allocation.

When a country is ready to introduce pharmaceutical regulation, work by WHO (1990) provides useful guidance for authorities with limited human, financial, scientific, and technological resources. To be effective, a small drug regulatory authority needs to operate within the national pharmaceutical laws and policies that have been established and must relate to other interested bodies, including organizations responsible for pharmaceutical procurement in the public sector and the national formulary committee. As mentioned, effectively enforcing pharmaceutical legislation requires national regulatory authorities and other government enforcement agencies, such as customs, police, and prosecutors, to work together. National regulatory agencies should also seek the cooperation of health professionals, pharmaceutical and consumer associations, and other interested parties through stakeholder workshops, meetings addressing specific issues, or other venues open to the public.

A drug regulatory authority's objectives can be accomplished effectively only if a mandatory system of licensing

products, manufacturers, importing agents, and distributors is in place. A small authority has limited capacity to undertake these tasks. For imported pharmaceutical substances, a small authority is dependent on information generated in the exporting country. The WHO certification scheme on the quality of pharmaceutical products moving in international commerce (WHO 2000) was designed to provide this information, although recommendations have been made on how to update the scheme (WHO 2008). As discussed in Chapter 19, this scheme must be supplemented by direct contacts with international agencies and other regulatory agencies to obtain necessary information; however, the certification scheme is only as good as the certifying authority. WHO's prequalification program provides information on approved sources for products related to HIV/AIDS, malaria, tuberculosis, and reproductive health.

Many national regulatory authorities do not make publicly available their regulatory policies, administrative procedures, guidelines, and criteria for decisions. Lack of transparency means that communication is probably lacking on medicine regulation between national regulatory authorities and their stakeholders. Moreover, transparency is required to make the agency accountable for its actions and to limit the influence of political pressures and personal favors in the decision-making process. Transparency will also contribute to the credibility and authority of communications between the agency and those affected by its actions: manufacturers, importers, distributors, health professionals, and consumers. An assessment tool is available to measure transparency in the pharmaceutical sectors (WHO 2009a) and a report describes the assessment of four

countries' pharmaceutical registration, selection, and procurement systems: Lao P.D.R., Malaysia, Philippines, and Thailand (WHO 2006a).

To increase the amount of information and communication, WHO is helping drug regulatory authorities develop websites with information on—

- Lists of approved medicines
- National pharmaceutical regulations
- Methods to ensure safe, efficacious, and rational use of specific medicines
- Lists of approved companies and their authorized activities
- Details of persons and institutions with responsibility for pharmaceutical regulation

WHO resources available for drug regulatory authorities include—

- A model website for drug regulatory authorities that aims to enhance communication and transparent dialogue among national drug regulatory authorities, industry, consumers, and health professionals (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/model_site/en)
- A list of recognized drug regulatory authorities' websites (http://www.who.int/entity/medicines/areas/quality_safety/regulation_legislation/ListMRAWbsites.pdf)
- A tool to assess regulatory authorities (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/assesment/en/index.html)
- Practical guidance for conducting a review (based on the WHO Data Collection Tool for the Review of Drug Regulatory Systems) (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/GuideAssessRegSys.pdf)
- A drug regulatory status database (http://www.who.int/hiv/amds/patents_registration/en/index.html)

In summary, the regulatory authority should be vested with legal powers to—

- Issue, vary, and revoke licenses for pharmaceutical products on grounds of quality, safety, and efficacy
- Ensure the safe and effective use of each product by controlling, through the terms of the license, the content of all labeling (including package inserts, associated prescribing information, and advertising) and the channels through which the product may legitimately be supplied
- Inspect and license all manufacturing premises, importing agents, wholesalers, distributors, hospital dispensaries, independent pharmacies, and other retail

outlets to ensure that they comply with prevailing regulations and guidelines

To implement these responsibilities, the authority must have the power to order that certain things be done and to prosecute those who disregard the law. To retain public confidence and respect, the authority must be seen as operating in an independent, authoritative, and impartial manner. It should be concerned exclusively with the determination of standards and the implementation of controls. Although it needs to work closely with the body responsible for public pharmaceutical procurement, it should not be responsible for procurement and should remain independent in its operations and decisions.

6.8 Evaluating the effectiveness of pharmaceutical legislation

Evaluating the effectiveness of pharmaceutical legislation and accompanying regulations is not always easy. The process of evaluation depends on the types of performance indicators and criteria used and on the availability of adequate data. The questions in the Assessment Guide at the end of this chapter provide a framework.

The most important factor in the effectiveness of pharmaceutical laws and regulations is the extent to which the legislative framework is in tune with national policy and the existing situation in the pharmaceutical sector. Changes in policy need to be reflected in the legislation and in its implementation.

Measuring the effectiveness of a law on pharmaceuticals is easier for certain elements than for others. For instance, the registration process can be evaluated in relation to quantitative targets and time schedules to see whether the agency is on schedule.

The degree of noncompliance with a law or regulation may suggest not only the need to take action against those responsible but also the desirability of identifying the causes of noncompliance: it may be related to technical defects in the law or in its wording, or to operational problems of implementation, such as lack of transparency or poor communication, which can be resolved. Enforcement personnel should periodically report on their perception of how the law functions and the types of problems encountered to facilitate any necessary revisions. Many legislative and regulatory provisions can be improved and updated when the legislation is sufficiently flexible to allow for modifications by the regulatory agency.

Responsibility for evaluating the effectiveness of a drug law often falls on the regulatory authority established by law for policy making, implementation, or both. The level of accountability and transparency under which the drug regulatory authority operates can be evaluated by examining

reporting requirements, external reviews of performance, processes involved with lodging complaints, and appeals procedures. Periodic self-evaluation to identify weaknesses in policy making and implementation activities is important. The body must devise its own systems to judge whether it receives sufficient feedback and whether its operational effectiveness can be improved. ■

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★ = Key readings.

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ASSESSMENT GUIDE

Policy, legislation, and regulation

- Is there a national medicine policy approved by the government? Is the policy suitable to regulate the market? When was it last updated?
- Is there a comprehensive medicine law? Is it appropriate? Is it a new law or a revision of an existing law? When was it last updated?
- Is the legislation flexible in allowing for the passage and revision of regulations in response to new scientific information and market changes?
- Is there a drug regulatory authority responsible for the promulgation of regulations and for enforcement? Does the necessary political will and funding exist to support it?
- Are regulatory policies, procedures, and criteria for decisions available to all stakeholders?

Medicine selection and registration

- Is there a system for medicine registration? Is this a notification procedure? A basic authorization procedure? A full registration procedure? Is periodic renewal required?
- Is medicine registration based on an assessment of a medicine's efficacy, safety, quality and truth of packaging information? Are pharmacological or therapeutic standards used?
- Are there different registration procedures for essential medicines, generic products, multisource drugs, or imported products from selected countries?
- Is the WHO certification scheme on the quality of pharmaceutical products moving in international commerce used systematically for the registration of imported medicines?
- Are relevant medicines procured from suppliers prequalified by WHO?
- Is there a system for the collection of data regarding the efficacy and safety (adverse effects) of marketed medicines?

Licensing, inspection, and control

- Do mechanisms exist for the licensing, inspection, and control of pharmaceutical personnel and for

manufacturing, distribution, and dispensing facilities?

- Do inspectors use a checklist for inspecting different types of pharmaceutical establishments?
- How many inspections were made during each of the last three years for the different types of pharmaceutical establishments?
- Is there an audit system to evaluate the inspection system?

Advertising and promotion

- Is there any specific regulation regarding therapeutic claims in drug labeling and promotion?
- Is there any legal provision for the compulsory use of generic names in medicine labeling and promotion?
- Are there controls on pharmaceutical promotion, and are these consistent with the WHO ethical criteria for medicinal drug promotion?

Compliance and enforcement

- What measures exist for enforcement of pharmaceutical laws and regulations? Are they enforceable administratively or through court actions? Are statistics available about compliance and enforcement?
- During the last three years, how many pharmaceutical products were eliminated from the register? How many batches of pharmaceutical products were recalled from the market?
- Is there a system for reporting pharmaceutical product problems? What types of and how many complaints were registered in the past three years, and what corrective measures were taken?
- How many violations have occurred with regard to pharmaceutical advertising and promotion in the past three years? What corrective measures were taken?
- Are there any statistics about the reaction of the industry and consumers to regulatory actions?

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