Ensuring the Quality of Medicines in Low-Income Countries

AN OPERATIONAL GUIDE

DRAFT FOR FIELD TESTING




U.S. PHARMACOPEIA

IN COLLABORATION WITH OTHER PARTNERS

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PREFACE

In 2002, Anthony F. Boni, Technical Officer for Pharmaceuticals in the Bureau for Global Health of the United States Agency for International Development (USAID), raised the idea of writing a manual to ensure the quality of medicines used by the public and private sectors in developing countries. Subsequent discussions with staff of the United States Pharmacopeia's (USP) Drug Quality and Information Program led to the development of this *Operational Guide to Ensure the Quality of Medicines in Low-Income Countries*. The guide was developed through a collaborative effort of the USP Drug Quality and Information Program; the Department of Medicines Policy and Standards of the World Health Organization; the Rational Pharmaceutical Management Plus Project; Program for Appropriate Technology in Health; Organon Pharmaceuticals; and the national medicines regulatory authorities of Malaysia, Uganda, Vietnam, and Zimbabwe.

Since 1820, USP has established the official standards of quality, purity, strength, and labeling for medicines used in the United States and Canada; today these standards are used in many other countries as well. The USP Drug Quality and Information program is a cooperative agreement between the United States Pharmacopeia and USAID to build local capacity in medicines quality assurance and control, and medicines information development and dissemination. USP has worked with USAID since 1992; the partnership now provides technical assistance to more than 20 developing countries. All partners involved in drafting this guide were invited to participate because they have expertise in supply management, quality control, national health programs, and national medicines policy development. It has been a wonderful group with whom to work—enthusiastic, committed, and talented.

One obstacle the authors encountered was their many locations scattered around the world. Would the authors merely draft their assigned chapters in isolation and submit them for inclusion in a textbook-style document, or should there be a group process of designing, developing, and reviewing the manual that would incorporate the expertise of all the authors into the style and objectives of the guide? The latter path was taken, and through electronic mail, conference calls, and periodic group writing workshops, this guide was created. Ideally, it expresses the viewpoints of all authors—many of whom have direct experience in assuring the quality of medicines for government health programs.

This document is labeled a *Draft for Field Testing*. USP DQI will field-test the guide and encourage other organizations and governments to use it and provide comments. The guide will be revised and published as a final document after one year of testing—although, in reality, such a manual can never be final; it must always be updated as new systems, policies, and technologies enter the equation.

I applaud USAID for supporting this effort and extend my appreciation to all the authors who contributed to the development of the guide. I hope it will be used widely and that the global health community will benefit by having secure knowledge that the medicines they use to prevent and treat disease will be of high quality, no matter where they are used.

Roger Williams, M.D.
Chief Executive Officer
United States Pharmacopeia

CHAPTER 1

Introduction

Health care professionals and patients assume the medicines they use are of good quality, but recent reports indicate that substandard and counterfeit medicines are widely available—especially in countries with limited regulations. This guide is dedicated to the people living without the protections of a highly developed health care infrastructure, strong law enforcement, and responsible regulation of the pharmaceutical industry.

Poor-quality medicines affect the lives of patients and nations alike. Patients who use poor-quality medicines remain ill longer and spend more time in health facilities, thereby increasing the burden to the health care system. When public health systems use poor-quality medicines, consumer confidence in public health services is undermined and families may turn to private medicine retailers, and spend a large proportion of their income on medicines (World Health Organization, 1999a).

Beyond immediate health outcomes, substandard medicines can exacerbate national and regional health problems, especially those associated with infectious diseases. Poor-quality medicines may contribute to antimicrobial resistance, which is an increasing problem for the treatment of tuberculosis and malaria. For example, use of substandard medicines to treat malaria can result in poor bioavailability or suboptimal dosing, which allows the malaria parasite to adapt before it can be killed. When a medicine used to treat a disease is no longer effective, a newer medicine is not always available to take its place. Many so-called neglected diseases, such as leishmaniasis, are still treated with medicines that have been around for decades. Use of substandard, narrow-spectrum antibiotics may lead practitioners to believe that the medicines are ineffective, and unnecessarily prescribe newer and more expensive broad-spectrum antibiotics, which places additional financial pressures on the health care system and the patient. When an important medicine is lost to resistance, entire prevention and treatment strategies must be reassessed. The process of researching and developing new medicines is both lengthy and costly.

The following practices will assure that high-quality medicines are always available:

- When medicine manufacturers use high-quality raw materials and follow current good manufacturing practices.

- When importers and distributors (wholesalers) of medicines store, transport, and distribute according to medicine regulatory agency-approved standards for maintaining product quality.
- When medicine dispensers follow recognized dispensing practices.
- When medicine regulatory authorities perform their core functions on a regular basis, such as registering medicine products, inspecting facilities, and performing laboratory testing and postmarketing surveillance for quality and adverse drug reactions.

To ensure that those involved in the manufacture and distribution of pharmaceuticals comply with accepted practice standards, governments must establish regulatory authorities and create a climate in which effective medicine quality is valued and ensured.

Poor-quality medicines are those that do not meet recognized standards for strength, quality, purity, packaging, and labeling. Medicines of poor quality may be legally registered as innovator or generic products, or they could be counterfeits—deliberately mislabeled for identity, strength, or source. In most countries, counterfeiting is a criminal offense; however, fines and penalties may be so minimal that they do not deter criminals.

International attention is focusing on the problem of poor-quality medicines for the health and economic reasons already mentioned. Guidance has been offered by the World Health Organization (WHO) and other international organizations, but few countries are able to allocate the resources and skilled personnel necessary to effectively implement the WHO recommendations. This guide is intended to help countries with limited resources and technical capacity to establish systems, facilities, personnel, and laws to ensure the high quality of medicines they register, import, purchase, store, distribute, and use.

This manual will provide guidance on the following aspects of quality assurance:

- Establishing a medicines registration system
- Monitoring local production of medicines
- Import controls
- Laboratory testing
- Medicines quality surveillance in remote areas
- Licensing for wholesalers and retailers
- Inspection services
- Enforcement of drug regulations.

Aim and Objectives

The goal of this guide is to provide practical advice to assist limited-resource countries to improve the quality of medicines that exist in their local markets and to ensure that medicines used in their national priority disease programs are of good quality. The guide is intended to assist program managers, donor organizations, and governments to select, purchase, and distribute only high-quality medicines, despite limited human and financial resources, weak infrastructures, and competing priorities. This document does not attempt to address all issues

within the pharmaceutical sector. Pricing, intellectual property rights, and new drug research, for example, are not discussed.

The guide also defines commonly used pharmaceutical terminology to facilitate better communication and cooperation among nations.

The guide will be linked to training courses and materials, and demonstration projects in product surveillance, basic testing methods, and good laboratory practices; the writing of specifications for procurement; the development of standard operating procedures; the use of pharmacopeial documents and reference standards; and other aspects of medicines quality assurance.

The guide has four specific objectives as described below.

Objective 1. To offer a tool for evaluating the strengths and weaknesses of existing medicine quality assurance processes and determining where to prioritize corrective actions in the short, medium, and long terms.

- To provide quality control options where gaps exist so current procurement and distribution can continue with product confidence.
- To provide tools for estimating investments required for specific components of quality assurance.

Objective 2. To assist local and international nongovernmental organizations to procure medicines of good quality.

- To provide unbiased guidance on how to develop procurement specifications and plan for appropriate selection of products and suppliers as well as pre- and postshipment inspection.
- To explain bioavailability and describe when and how the study must be assessed.
- To explain bioequivalence (BE) and recommend when BE data should be required and how to evaluate BE data for multisource products.

Objective 3. To provide clear directions to health care practitioners, pharmacists, and retailers regarding storage and handling of medicines to maintain product stability.

Objective 4. To help governments regulate their local pharmaceutical industry.

- To determine where, when, and how often to inspect for good manufacturing practices (GMP); provide references to acceptable GMP guidelines; and set schedules and incentives for GMP compliance.
- To provide references to guidelines for planning and organizing a quality assurance system within a pharmaceutical factory.
- To encourage interaction and communication among medicines regulatory authorities, national health program managers, nongovernmental organizations, and manufacturers to resolve problems or conflicts related to licensing, registration, and marketing.

How To Use This Guide

This guide provides a sequential overview of major issues that ensure the quality of medicines in resource-limited settings. It contains detailed explanations of fundamental concepts, principles, definitions and use of terms, checklists, and practical examples to implement effective changes in quality assurance.

Most chapters offer checklists at the end of the chapter to self-assess existing policies, procedures, facilities, and human resources, and to identify gaps that need to be corrected or improved. For example, if a registration system is weak, additional postmarketing quality surveillance may be necessary. However, as a medicines registration system develops and becomes more effective, less testing may be needed.

Several chapters offer a general checklist to guide readers through the process for decision-making, designing and planning a quality assurance/quality control (QA/QC) framework, and implementing and improving specific areas such as premarketing control, laboratory testing, procurement, storage, and distribution. For a more comprehensive assessment of the status of a country's QA/QC capacity and performance, readers are directed to the rapid assessment tool (Chapter 12), which will aid decision-makers and implementers to successfully identify, prioritize, and implement the guide.

Access to this guide will be available electronically on the following websites: United States Pharmacopeia Drug Quality and Information (USP DQI) at http://www.uspdqi.org, World Health Organization Essential Drugs and Medicines Policy at http://www.who.int/medicines, Management Sciences for Health Rational Pharmaceutical Management Plus (RPM Plus) program at http://www.msh.org/rpmplus, and Partners for Appropriate Technology in Health (PATH) at http://www.path.org.

CHAPTER 2

Ensuring Medicines Quality: Key Players and Their Responsibilities

Medicines in the form of herbs, minerals, and animal parts have been essential throughout history for the treatment of illnesses or to prevent disease. Experience indicates that because healers who also produced the medicines sometimes used defective and adulterated medicines, societies were able to exercise some control over the dispense and use of these products (World Health Organization, 1999b).

Medicines Quality

Advancements in science and technology have enabled humankind to produce a plethora of medicines through a variety of chemical and biological processes. Contrary to ancient times, the modern process of medicine development involves several factors, and as a result, issues of quality, safety, and efficacy have become more profound.

Quality is built into a medicine during its design, development, and manufacture. Manufacturers are primarily responsible for the quality of the medicines they produce by following the tenets of good manufacturing practice (GMP). After a product leaves the manufacturer's premises distributors, procurement agencies (purchasers), dispensers, and users are responsible for maintaining the quality of the product through proper storage, transport, distribution, dispensing, and use.

National governments are responsible for ensuring that manufacturers comply with current GMP requirements. This may present a challenge for countries with limited resources. Guidelines for meeting current GMP are available from the World Health Organization and from countries with progressive drug regulatory agencies.

Key Players

This section discusses the persons and groups who have primary responsibility for maintaining medicines quality.[1] Figure 2.1 depicts the main players involved in the supply and control of medicines.

Government leaders and policymakers

National government leaders and policymakers are responsible for defining national medicines policies. Few low- and middle-income countries include quality assurance in their national medicines policies. The establishment of quality assurance mechanisms under national policies has led to notable successes in some countries.

Experience in Australia, Canada, and the United States, for example, has shown that adequate legislation and its enforcement result in fewer poor-quality medicines and greater public confidence in the quality of the medicines (Ratanawijitrasin and Wondemagegnehu, 2002). In contrast, when the pharmaceuticals market is poorly regulated due to inadequate legislation or weak enforcement, counterfeit and substandard medicines proliferate (World Health Organization, 1999a).

In brief, national leaders and policymakers have the following responsibilities:

- Formulating and updating legislation and regulations to cover all aspects of national pharmaceutical trade and use. Legislation and regulations form the foundation of assuring medicine quality.
- Establishing a national medicines regulatory authority (MRA) that incorporates the medical, scientific, and technical knowledge and skills necessary to control medicine quality. For an MRA to function properly a national government must:
  - Provide appropriate organizational structure
  - Assign qualified, trained, competent personnel
  - Allocate adequate and sustainable financial resources
  - Provide the necessary facilities and tools
  - Enact legislation to empower the MRA.

If these resources are inadequate or lacking, an MRA will not be able to properly perform its functions, which may lead to substandard and counterfeit medicines in the marketplace.

National medicines regulatory authority

An MRA is responsible for ensuring the safety, efficacy, and quality of imported and locally produced medicines. Their authority should encompass the public and private sectors alike. An MRA's key activities include the following:

- Registering medicinal products (i.e., authorizing the marketing of medicines).
- Licensing pharmaceutical establishments (manufacturers, importers, distributors/wholesalers, and retailers).
- Issuing, amending, and revoking registration for products due to unacceptable quality, safety, or efficacy, including product recall notification.

- Inspecting manufacturing, distribution, and retail premises for compliance with GMP and good dispensing practice.
- Monitoring quality and safety of medicines in the marketplace (postmarketing).
- Controlling activities designed to promote and advertise medicines.
- Approving clinical trials.

Countries with limited economic and technical resources may prioritize these activities. The first priority should be the licensing of importers, wholesalers, and retailers. This could occur in a five-step process:

1. License importers, wholesalers, and retailers (pharmacies and drug stores).
2. Require registered importers or wholesalers to notify a central body which products they intend to import or which ones they have already imported.
3. Recognize the Pharmaceutical Inspection Cooperation Scheme (PICS) and International Conference on Harmonization (ICH) registrations and WHO-prequalified products.
4. Evaluate generic product applications. Register manufacturers and perform GMP inspections in exporting and receiving countries.
5. Perform a full evaluation of medicines registration (see Figure 4.3).

Procurement organizations or purchasers of medicines

Those responsible for procuring or purchasing medicines have the following responsibilities:

- Holding an authorized license issued by the MRA and operating under the requirements of the license.
- Assigning a technically qualified person to oversee quality assurance activities.
- Developing standard operating procedures to guide procurement, including defining the specifications of products to be purchased.
- Ensuring that the products they purchase are approved by the MRA, if one exists.
- Applying for product registration, if products are not registered with the MRA.
- Inspecting each consignment, where feasible, to check for completeness and compliance with purchase order specifications and requirements.
- Storing, transporting, and distributing medicines according to good practices and MRA requirements.
- Maintaining records of products purchased and distributed, and establish a product recall system.
- Retaining samples of products procured and distributed.

Manufacturers of pharmaceutical products

Drug manufacturers have a variety of responsibilities in ensuring the products they manufacture are legal and safe. Among their responsibilities are the following:

- Applying for an MRA license and to operate under the requirements of the license.
- Assigning or recruiting a technically qualified person to oversee quality assurance activities.
- Assuring that the raw materials, including the active pharmaceutical ingredients, excipients, and packaging materials used in production and packaging, are from reliable sources.
- Producing products in accordance with the current code of GMP and national medicines regulations.
- Ensuring that products are distributed only to licensed or approved establishments, including wholesalers, distributors, health facilities, pharmacies, and retail outlets.
- Keeping records of products distributed or sold to ensure traceability.
- Establishing a record of complaints and a recall system.
- Establishing and maintaining ethical marketing standards.

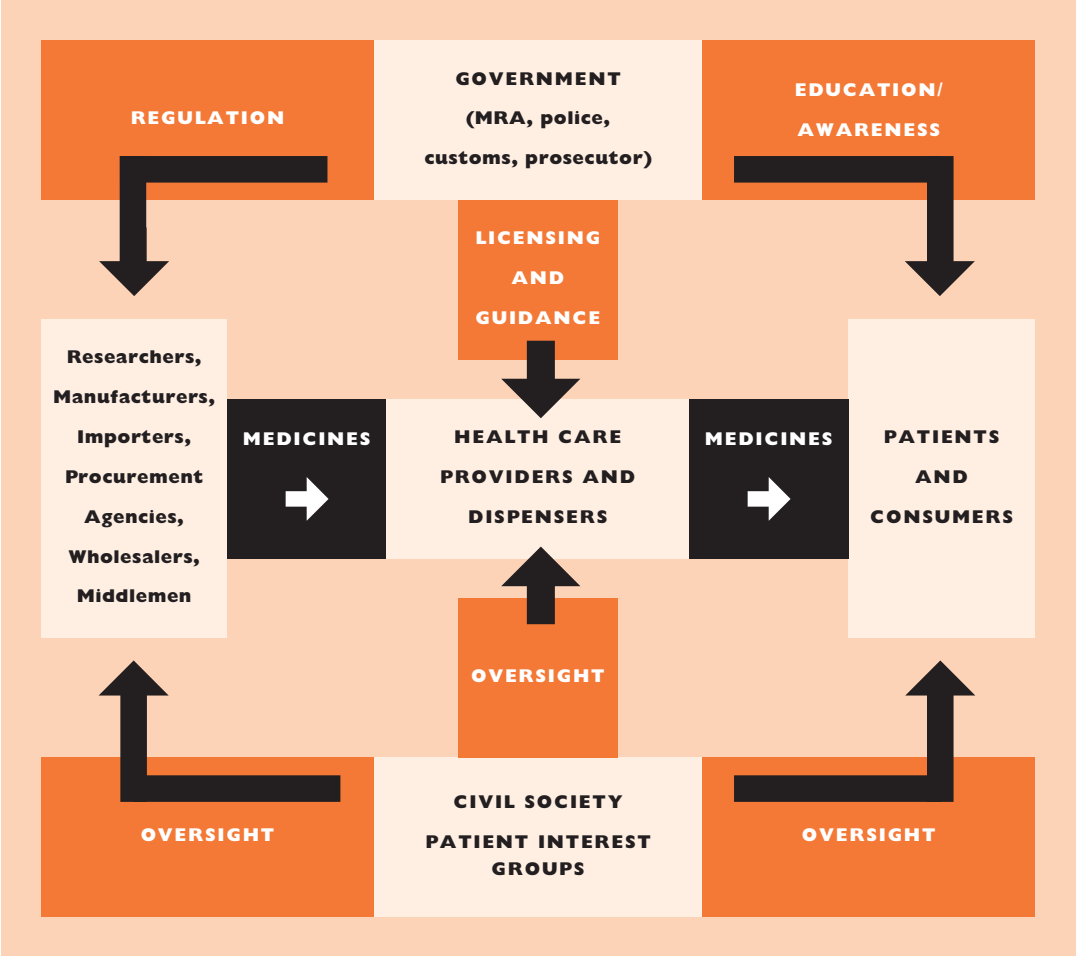

Figure 2.1
Key players and their responsibilities for ensuring medicines quality

National disease programs

Personnel in a country's national disease program are responsible for following the national health and medicines policies, ensuring that medicines in use are approved by the relevant authority, including the MRA, and for adhering to the responsibilities listed above for procurement organizations if they are involved in the procurement, distribution, and supply of medicines.

Medicines prescribers

Physicians who prescribe medicines are responsible for doing so according to nationally or internationally accepted standards, for informing patients how to safely take medicines, and for advising patients to purchase medicines only from licensed retailers.

Medicines dispensers

Because individuals who dispense medicines have direct contact with consumers and patients, they play a vital role in ensuring they purchase, stock, and dispense only high-quality medicines. Their responsibilities include the following:

- Ensuring a safe, clean, and secure dispensing environment.
- Receiving, verifying, and understanding prescriptions.
- Dispensing the correct medicines in correct dosage forms in the correct quantity, and with the correct instructions only to those patients who have been prescribed pharmaceuticals.
- Recording the actions they have taken to national and other authorities.

Patients, consumers, and patient advocacy groups

Persons who use medicines also have responsibilities. They include the following:

- To purchase or obtain medicines only from outlets or health facilities that are properly authorized or licensed to dispense medicines.
- To physically and visually examine the medicines they purchase or receive to ensure they receive the correct dosage, and to review the name of the medicine, the strength, and expiry date.
- To ensure that medicines bear appropriate labeling and instructions regarding their use.
- To follow the advice provided by dispensers and physicians, as well as instructions on labels.
- To store medicines according to the instructions given by dispensers or according to the pharmaceutical label.
- To use only medication or drugs that have not expired or physically changed (e.g., to ensure that medicines have not discolored or deteriorated).
- To inform the dispensing outlet or physician if a product has changed in appearance or form.

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[1] Product designers and developers are important players in medicine quality, but this guide does not include them as a target audience.

CHAPTER 3

Policy and Legal Framework for Ensuring Quality of Medicines

This chapter describes the purpose, development, and elements of a medicines policy, with emphasis on quality assurance. The need for developing a legal framework to implement a national medicines policy is discussed. Also explained are elements of national medicines legislation and regulations required to implement such legislation.

What Is a National Medicines Policy?

A national medicines policy is a written document that expresses a government's commitment to set medium- and long-term goals in the pharmaceutical sector. A national medicines policy is an integral part of a national health policy, and defines the roles and responsibilities of the main players in the public and private sectors. A national medicines policy also provides the framework within which the various activities of the pharmaceutical sector can or will operate (World Health Organization, 2002c).

The format and content of national medicines policies vary from country to country. For instance, the national medicines policies in Bhutan, Bangladesh, Indonesia, Laos, and the Philippines are expressed in single, comprehensive documents that outline the various activities of the pharmaceutical sector. Other countries have policies that are expressed in several separate documents, each covering a particular activity or area (World Health Organization, 2004).

General objectives

A national medicines policy should, at a minimum, encompass issues of access, quality, and rational use.

ACCESS

A national medicines policy should focus on the diseases usually associated with poverty, such as malaria, HIV/AIDS, and tuberculosis, and those affecting children and women. To guide this focus, national strategies often finance the supply of medicines and make these medicines affordable for all citizens. National distribution systems may be designed to ensure that drugs are available at all levels in the supply chain.

QUALITY

Regulatory mechanisms and quality assurance standards are designed to define expected pharmaceutical standards for quality, safety, and efficacy.

RATIONAL USE

Therapeutically sound and cost-effective policies for the use of medicines by health professionals and consumers must exist.

ADDITIONAL CONSIDERATIONS

Depending on a country's health-related goals, political priorities, and economic goals, a national medicines policy may have specific objectives. For example, to ensure regular access, a national government may include an objective in its policy that seeks to increase national pharmaceutical production capacity.

Key components

A national medicines policy has at least nine key components, as outlined below.

SELECTION OF MEDICINES

Choosing the medicines to be included in a national medicines policy should be based on the concept of essential medicines that promote equity and that establish priorities for a nation's health care system. The concept stresses the use of a limited number of carefully selected medicines on the basis of agreed therapeutic guidelines. In theory, this concept should lead to a better supply of drugs, rational prescribing, and lower costs.

AFFORDABILITY

Affordable pricing is a prerequisite for ensuring equal access to essential medicines. In establishing national medicines policies, governments are advised to adopt tariff reductions, generic policies, and price negotiation to guarantee affordability.

MEDICINES FINANCING

Appropriate and realistic financing will lead to improved access to essential medicines. Key issues to consider in medicines financing schemes include a commitment to improving efficiency, increased funding for priority diseases and treatments for vulnerable groups, and the promotion of health insurance schemes.

SUPPLY SYSTEMS

A reliable supply of medicines includes a public–private sector mix in medicines supply and distribution, sound procurement policies, contingency measures for acute emergencies, and disposal of unwanted medicines.

REGULATION AND QUALITY ASSURANCE

A national medicines policy must aid in the establishment of a medicines regulatory body that will develop and implement legislation to ensure the quality, safety, and efficacy of medicines.

Governments must be committed to medicine regulation to ensure a sound legal basis and sufficient resources for an effective national medicines regulatory authority, and that authority must have transparent decision-making processes. There must be commitment to good manufacturing, inspection, and law enforcement practices.

RATIONAL USE

Patients should receive medicines appropriate to their needs, in appropriate doses, for the appropriate period, and at the lowest cost to them and their community. Therapeutic guidelines, support for therapeutics committees, promotion of rational medicine use, and continuing education for health care providers and consumers will promote rational use.

RESEARCH

Operational research is important for assessing a medicines policy's effect on national health care delivery systems and for identifying problems related to medicine supply.

HUMAN RESOURCES

Policies and strategies must be defined to ensure that a sufficient number of trained and motivated personnel are available to effectively implement a national medicines policy. Well-funded, ongoing training programs focused on career planning and advancement are essential.

MONITORING AND EVALUATING

Government commitment to the principles of monitoring and evaluation must be defined in national medicines policies, and should include an independent assessment of the impact of a national medicines policy, as well as indicator-based surveys of the progress and success of the policy.

Legal framework

The mere existence of a written medicines policy does not guarantee the transformation of the policy into action. There must be qualified human resources and adequate financial resources, as well as facilities, laws, and authorities with legal powers to enforce the provisions of the policy, the legislation, and the regulations. Systems must be in place to monitor how the national policy is implemented, to enforce the legislation and the regulations, and to ensure that various activities are carried out in a transparent manner. Those responsible for implementing the policy are accountable to the government, the public, and the individual citizens.

Legislation and regulations are needed to ensure that manufacturing, importing, exporting, distributing (wholesale and retail), and dispensing are performed according to safety, efficacy, and quality norms and standards.

Drafting National Medicines Legislation

A national medicines policy is developed in consultation with all relevant stakeholders and beneficiaries of the policy. Such consultation helps ensure collective ownership of the final policy by government officials, manufacturers, procurement organizations, and dispensers, and enhances cooperation and collaboration among all parties when the policy is implemented.

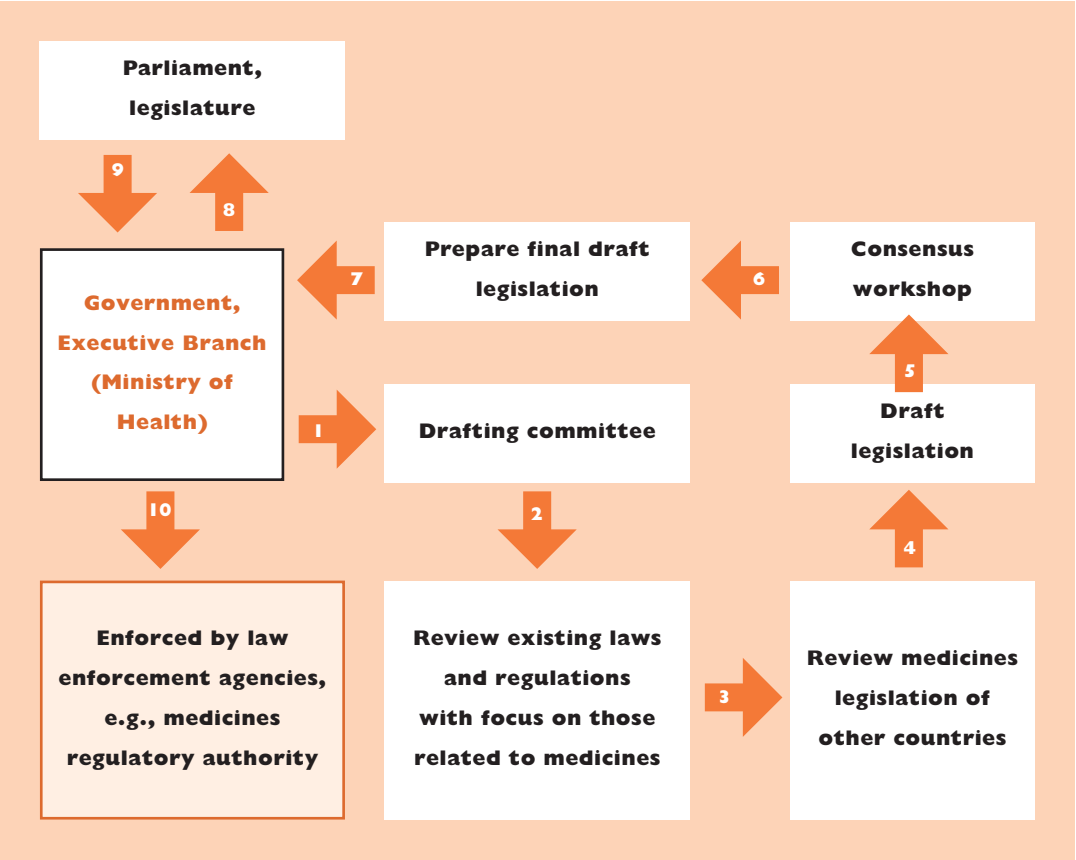


Figure 3.1
A model for developing national medicines legislation

Medicines play a substantial role in a country's health policy, and it is important that a national medicines policy be developed within the framework of the national health policy so that it is consistent with the broader national objectives. On the other hand, the health policy, and the level and nature of the health care services being provided, help shape the national medicines policy and define the range of choices and options.

Once a government adopts a national medicines policy, people with appropriate technical and legal backgrounds must discuss and prepare a legislative draft and build consensus. Those given this responsibility should include members of civic and consumer groups. The final draft legislation is submitted to the government for debate, adoption, and enactment.

Drafting process

The process of promulgating national medicines legislation (Figure 3.1) involves the following steps:

1. The executive branch of government is responsible for health care issues. The Ministry of Health establishes a committee of experts in drug regulation, public health, and law, as well as civil society and consumer groups.
2. The committee reviews existing national laws and regulations to identify legal provisions that address medicines. This review process helps prevent any overlap or duplication of duties and responsibilities of key responsible agencies in pharmaceuticals.

3. The committee reviews the medicines legislation of other countries to gain insight regarding other legislation, regulations, and policies.
4. The committee drafts the legislation.
5. The committee organizes one or more workshops in which stakeholders discuss the draft legislation and attempt to reach consensus.
6. The committee prepares a final draft of the legislation.
7. The drafting committee submits the final draft legislation to the Ministry of Health.
8. The Ministry of Health submits the draft legislation to the legislative branch of government.
9. The legislative branch of government approves the legislation and returns the proposed policy document to the Ministry of Health.
10. The Ministry of Health implements the legislation through a medicines regulatory authority.

Content of legislation

National medicines legislation should be comprehensive, incorporating all components of the national medicines policy that a government wishes to regulate. The purpose of the legislation, the categories of medicinal products to be regulated, and related activities should be defined. These processes generally include manufacture, importation, exportation, wholesale and retail distribution, supply, donations, and promotion.

Medicines legislation should identify these types of issues:

- Goals and objectives
- Categories of medicinal products and activities to be regulated
- Governing body responsible for enforcing the legislation
- Roles and responsibilities of the parties involved in the supply of medicines
- Qualification standards to be met by those who handle medicines
- Norms, standards, and procedures to be followed by those engaged in the supply of medicines
- Terms and conditions under which licenses will be awarded, suspended, or revoked
- Appointment of inspectors and their powers
- Legal sanctions and administrative measures.

CHAPTER 4

Regulatory Systems for Medicines

A national medicines regulatory authority (MRA) ensures that pharmaceutical products being sold in a country conform to acceptable standards of quality, safety, and efficacy. An MRA guarantees that all premises and practices employed in the manufacture, storage, importation, distribution, selling, and promotion of medicines conform to such standards until they reach their end users.

Many low-income countries cannot, however, ensure the safety, efficacy, and quality of medicines circulating in their markets. In 2003, the World Health Organization reported that only about 20 percent of countries had well-developed and operational medicines regulations. Of the remaining countries, only half had regulations of varying capacity and development, and 30 percent had very limited medicines regulations (World Health Organization, 2003b).

The absence of effective medicines regulations can lead to the proliferation of harmful, ineffective, substandard, and counterfeit medicines. The rapid introduction of high-technology medicines into import, export, and distribution networks, including e-commerce, increasingly challenges the capabilities of MRAs to ensure the safety, quality, and efficacy of medicines.

Medicines Regulatory Authority

An MRA ensures that marketed medicinal products (pharmaceuticals and biologics, including vaccines, blood products, and others) are acceptable in quality, safety, and efficacy.

Minimum functions of an MRA

Medicines regulatory authorities have responsibility for a variety of national-level functions. Among the most important are these:

- Evaluating and registering medicinal products.
- Inspecting and licensing manufacturing premises, importing and exporting agents, distributors, and wholesale and retail outlets.

- Overseeing quality control.
- Conducting postmarketing surveillance activities.
- Disseminating information on medicines.

Factors in effective regulation

Several factors contribute toward promoting good regulatory practices. For example, a national government shows its political will and commitment to implement and oversee regulations with strong public support, and strives for an adequate supply of medicines at affordable prices. An MRA must have the ability to work closely with other governmental law enforcement agencies, such as the customs service and national, provincial, and local police forces. A strong, functional MRA also depends on a nation having a sufficient number of qualified and experienced pharmaceutical and other professionals working in the pharmaceutical sector.

An MRA needs to have a clear vision, mission, goal, and strategy, and its functions should be supported by adequate legislation and regulations. To function properly an MRA also needs an appropriate organizational structure and facilities, clearly defined roles and responsibilities, and adequate and sustainable financial resources, including resources for staff retention and development.

In addition, to support its functions, an MRA must develop appropriate standards, guidelines, and procedures, although existing guidelines and procedures in use by more advanced regulatory agencies such as the World Health Organization, and programs such as the Rational Pharmaceutical Management Plus program (RPM Plus) and the United States Pharmacopeia Drug Quality and Information program (USP DQI) can be adapted for national use in the early stages of drug regulation. Regulatory work must be performed with accountability and transparency. Public accountability requires that information on decisions made by an MRA be available and accessible to the public. This may include negative decisions in the case of sanctions, recalls, denials, alterations, revocation of operating licenses, and public health warnings.

A checklist for establishing an effective MRA appears at the end of this chapter (Checklist 4.1).

ORGANIZATION AND MANAGEMENT

To achieve appropriate regulatory objectives, governments must establish strong MRAs with sound, yet realistic organizational structures and legal powers. The management capacity of an MRA in low-income countries is usually weak, and often, written guidance is not available for staff regarding principles, practices, and methods they should follow (World Health Organization, 2003b).

Figure 4.1 presents the minimum organizational structure of a national MRA, and Figure 4.2 presents an adaptation of the organizational structure of Malaysia's Pharmaceutical Control Bureau, showing its organizational structure and management authorities.

OPERATION AND FUNCTION

To function properly, an MRA needs a strategic plan with a clear vision and mission, objectives, strategies and targeted time frames for meeting them, expected outputs, and performance indicators. A clear sense of direction, good strategy, and effective implementation of strategic plans will foster success. Annual work plans and self-assessment programs will help identify program weaknesses.

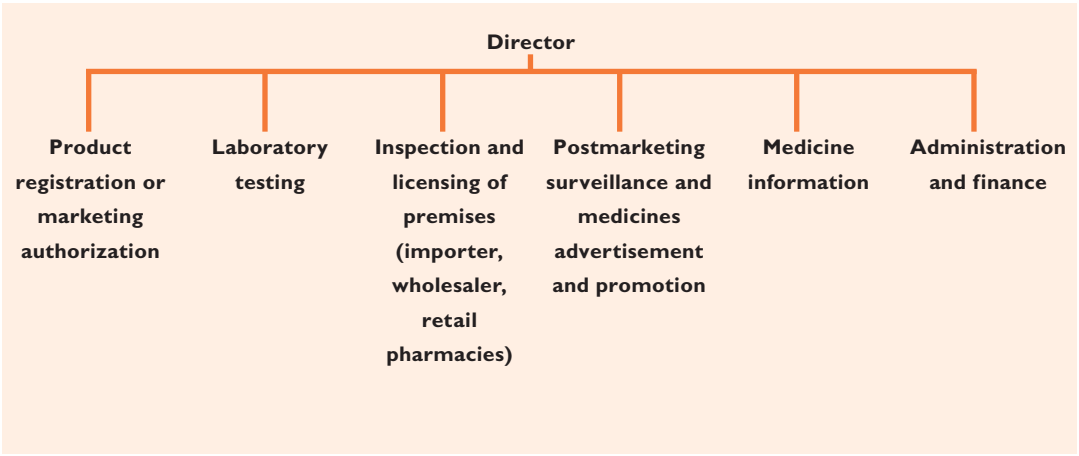


Figure 4.1
Minimum functional structure of an MRA

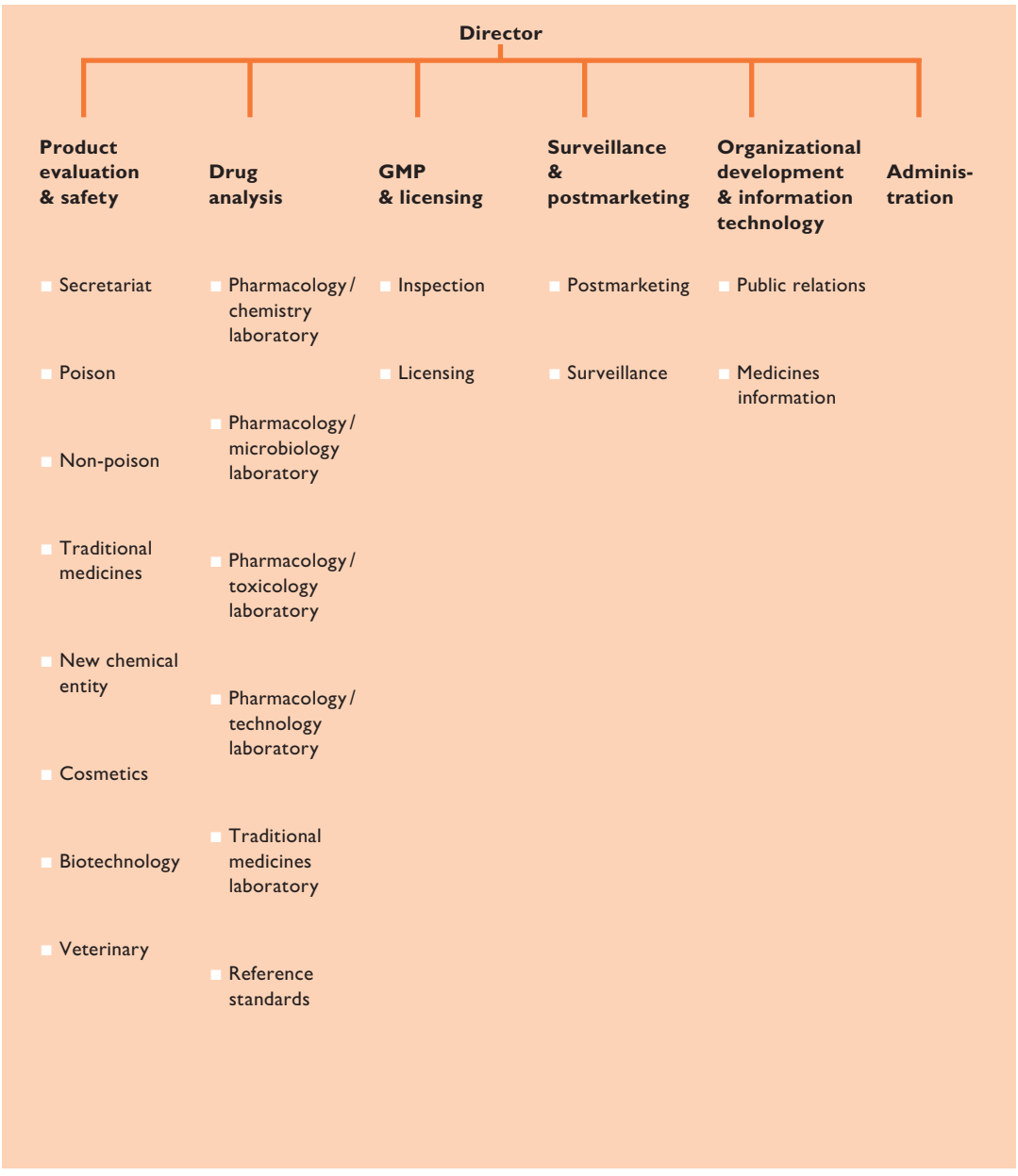


Figure 4.2
Organizational structure of an advanced national MRA
Source: Adapted from National Pharmaceutical Control Bureau, Malaysia, 2004.

Legislation forms the foundation of a nation's legal authority to regulate medicines, but guidelines, checklists, forms, manuals, and standard operating procedures are useful tools that enable an MRA to function effectively and efficiently.

Regulatory tools should be written to guide regulatory practice and be made publicly available to ensure the MRA's transparency. The Internet also offers a powerful tool for disseminating information quickly and globally.

Governments should ensure that MRAs are structurally and functionally independent of the agencies or bodies that are responsible for import and export, and management of the national medicines supply system. An MRA should regulate these agencies and apply regulatory controls to the public and private sectors. The same regulatory standards should be applied to medicines meant for domestic use as for export.

Human and financial resources

Adequate and sustainable resources are necessary for efficient and effective implementation of regulatory requirements. Table 4.1 identifies the primary types of resources required and the roles they serve.

Table 4.1 MRA resource requirements

Resource	Optimal Function
Personnel	Regulatory activities (e.g., licensing and registration) Monitoring, inspecting, and surveying enforcement
Physical and infrastructure	Office space for regulatory and enforcement personnel Computers, software, and office equipment Quality control laboratories Vehicles for distribution, inspection, and enforcement activities
Technical	Pre-service and in-service training Data collation Information dissemination
Financial	Capital and recurrent expenditures Technical programs Payments for consultants Publications (forms, licenses, pharmacopoeia)

Source: *Jayasuriya,* 1985.

Appropriate levels of human and financial resources are critical for successful medicines regulation. MRAs should employ personnel with specialized knowledge and skills who will not be susceptible to the commercial interests of stakeholders. Mechanisms should be put in place to ensure that staff members have current knowledge and expertise in specialized areas through on-the-job or professional training.

In most limited-resource countries, MRAs suffer from a shortage of qualified personnel because of their inability to offer attractive remuneration and incentives. The minimum number of personnel an MRA needs will depend on the scope of activities and the workload involved. MRA staff should receive adequate compensation and be governed by legislation that

minimizes conflict of interest; for example, MRA staff usually should not be allowed to hold dual employment or to perform contractual work with a medicines manufacturer or dispenser, or other private concern that could present the appearance of a conflict of interest.

Financial resources can be acquired annually through government allocations, donor agencies, or accrued revenue obtained from medicines regulatory activities. Financial resources should adequately cover staff salaries, facilities management, and special services by outside or contracted agencies, administrative operations, and human resource development.

Government resources alone are generally insufficient to ensure that medicines regulation is sustainable and effective (Ratanawijitrasin and Wondemagegnehu, 2002). Governments may need to revise their medicines legislation to introduce a fee system that reflects the real costs of the services they provide. However, special considerations, such as fee reduction or fee exemption, should be made for essential medicines.

Medicines Evaluation and Registration

In most developed countries, before medicines are approved for market distribution and human use, they are evaluated for quality, efficacy, and safety. This evaluation process involves screening and reviewing product information and data. Each application is submitted in the form of a product dossier along with appropriate fees and samples for laboratory testing.

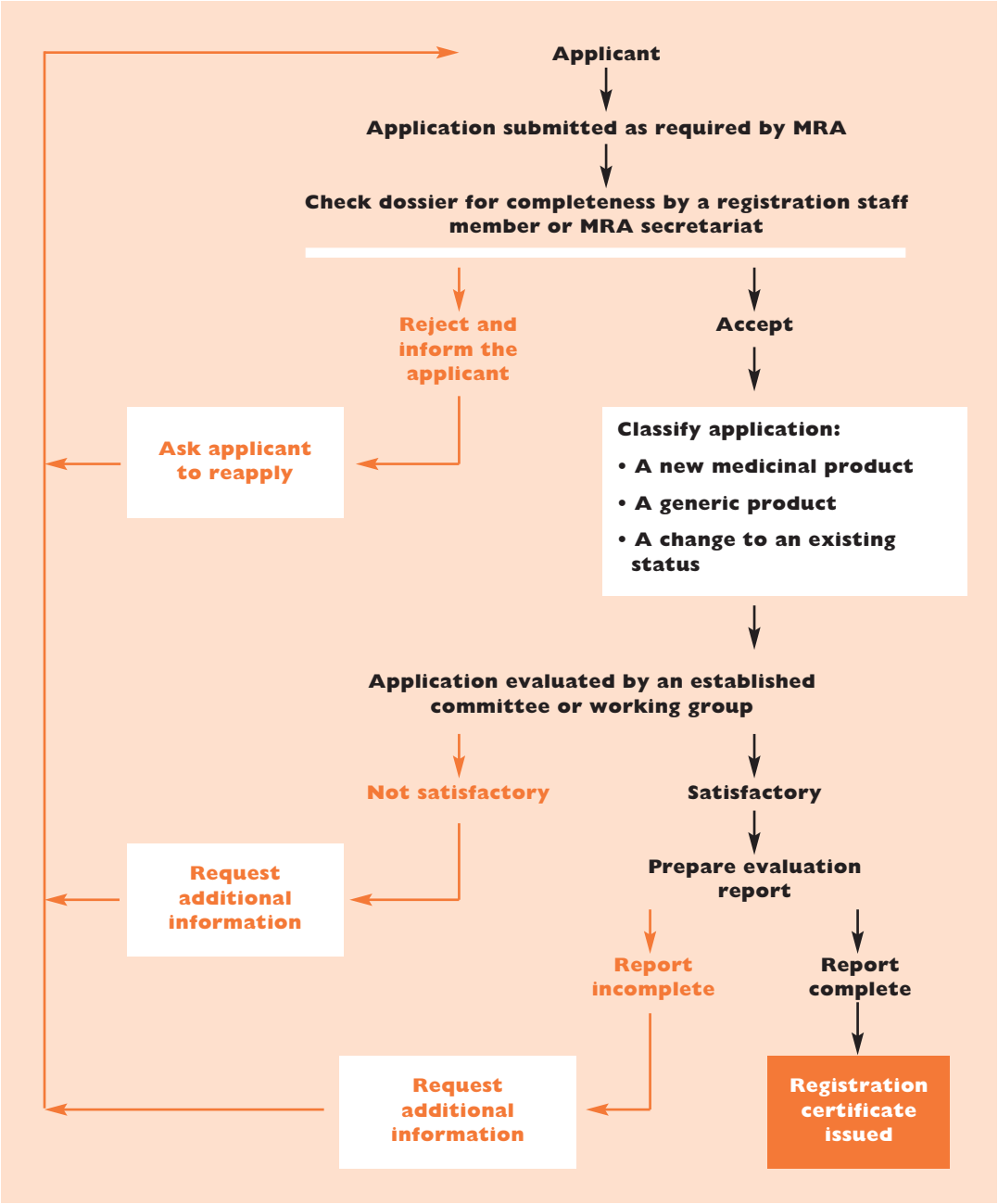
An MRA is usually responsible for establishing product registration guidelines and application forms. Countries with very limited resources may, however, wish to adopt the more pragmatic approach of relying on registration that has already occurred in countries with well-developed regulatory systems. The guidelines generally should contain instructions to help applicants, manufacturers, and exporters who intend to market their products prepare a proper product dossier. Figure 4.3 illustrates a typical registration process by depicting the relatively advanced registration process used by Malaysia's MRA, its National Pharmaceutical Control Bureau.

Components of a dossier for MRA evaluation

Applications may be filed to market (1) a new medicine, or (2) a generic medicine, including a banded generic product. A new medicine is one that has never before been registered and marketed in the country. A new medicine can also be considered one for which the dosage form or route of administration has changed although the medicine has been previously marketed in the country. A generic medicine (including a branded generic product) is one that has been promulgated in an official standard by an MRA—a generic drug is identical, or bioequivalent to a brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use (United States Food and Drug Administration, 2005); it is usually manufactured without a license from the innovator company and marketed after the patent or other exclusivity rights have expired. Supplementary applications may also be filed to change, add, or cancel approved contents or items in a pharmaceutical product, or to alter the approved clinical study, formulation, packaging, or labeling.

Dossiers submitted for MRA evaluation of generic medicines generally contain the information outlined below.

Figure 4.3
Flow chart of medicines registration



APPLICANT INFORMATION

Applications seeking approval to market a medicine must include an applicant's name; physical, postal, and electronic addresses; and telephone and fax numbers. Applicants should hold professional qualifications according to current regulations, such as registration as a pharmacist or pharmacy assistant with two years of pharmacy practice experience. Applicants should possess adequate financial resources to operate their business to prevent registration certificates from being transferred to another applicant that is not GMP-compliant (Zhen, 2003). Finally, applicants should hold legal entity status in the country and maintain a proper street address. Applicants who maintain an address outside the country should maintain a branch or agency in country that is duly recognized by the MRA to manufacture, import, .or procure pharmaceuticals.

PRODUCT INFORMATION

Information about a product being proposed for marketing and human use must include the product's name, strength, dosage, form, and therapeutic classification and a description of the product. The product and the packaging submitted with the dossier must precisely match those described in the product dossier.

The labeling on the immediate (primary) packaging should conform to national requirements. The following information for the sample submitted should be assessed: language used, international nonproprietary name (INN) or generic name, quantities of active pharmaceutical ingredients (APIs), manufacturing and expiry dates, batch or lot number, storage conditions, and name and address of manufacturers. Product information, such as prescribing leaflets, should also be checked for accuracy and ease of understanding.

MANUFACTURER INFORMATION

The product manufacturer's name and all physical addresses must be declared. Domestic manufacturing sites should be inspected by the MRA for current good manufacturing practice compliance before the product is registered.

PACKAGING MATERIAL SPECIFICATIONS AND PRODUCT COMPOSITION

Detailed specifications of the primary (inner) container and closure system and its suitability for the product are to be examined. The product formula—APIs and inactive ingredients—must be provided by the manufacturer. Approved INN names, chemical names, and molecular formulae for APIs must be provided, and reasons for including inactive ingredients must be stated.

CHEMISTRY AND PHARMACEUTICAL ASPECTS

A detailed explanation of manufacturing processes for the product, including equipment used and in-process controls, should be stated in the dossier. The dossier should contain certificates of analysis of the raw materials showing test results obtained by the raw material supplier and the manufacturer of the finished product. For raw materials, including APIs that do not have pharmacopeial monographs, the dossier should provide specifications (e.g., testing methods and procedures for identification, assay, impurity, and acceptance criteria) required for batch release control. For raw materials for which pharmacopeial monographs exist, the dossier should specify precisely what pharmacopeial specifications were used in quality testing.

For finished products, the specifications and limits described in the dossier must conform to the official pharmacopeial monograph, if one exists. If no official monograph exists, the specifications provided for the finished product should include a description, identification, assay, impurity profiles and limits, and all other tests and parameters relevant to the dosage form. If nonpharmacopeial or manufacturer's in-house test methods and procedures are used, a validation report for the method of analysis used should be provided. The validation report should include studies for parameters such as accuracy, repeatability precision, selectivity, linearity, and range and limits of detection. Laboratory test reports should indicate data from spectrograms and chromatograms for both the sample and reference chemical substance.

COMPLETE BATCH MANUFACTURING RECORDS

A copy of the complete batch manufacturing record should contain information for a single batch made at the declared manufacturer's site:

- Raw materials and packaging materials requisition and weighing records

- Processing records, including date and time of commencement and completion of each stage
- Line clearance records for beginning and ending activities of each critical production and packaging stage
- Packaging records
- In-process control and yield reconciliation records at all relevant stages during batch production and packaging
- Temperature–time charts for each sterilization cycle in the batch
- Finished product analytical report or certificate of analysis for the batch
- The batch manufacturing record, which should be checked for consistency with the composition of the product and manufacturing procedure declared by the applicant.

STABILITY STUDIES

Evidence of a finished product's stability should be included in the dossier. The products should be tested in the packaging intended for marketing. The type of stability study (i.e., either accelerated or real-time) that was used should be specified.

The test samples—from pilot or production batches—should be chosen from at least two different batches for stable active ingredients, and from at least three different batches for unstable active ingredients, as defined by the World Health Organization. Shelf-life determination should be based on the least stable batch.

Applicants should provide a detailed stability study protocol that was used with the accompanying summary of the results. The protocol should conform to the WHO recommendation for stability studies. Conclusions about the proposed storage conditions, shelf-life, and in-use storage conditions should be clearly stated in the dossier. The MRA should verify the consistency of the claimed shelf-life in the dossier with the in-use storage conditions and the shelf-life of the samples received.

For products with active ingredients that are new chemical entities, and for modified release products, the guidelines of the International Conference on Harmonization should be followed.

PRODUCT REGISTRATION STATUS IN THE COUNTRY OF MANUFACTURE AND OTHER COUNTRIES

Original or certified copies of the manufacturing license, GMP certificate, and product license or marketing authorization, together with the certificate of a pharmaceutical product moving in international commerce as recommended by WHO, should be submitted (World Health Organization, 1994).

THERAPEUTIC INDICATIONS

The main indications, side effects, adverse reactions, and contraindications of the product should be clearly stated in the dossier.

BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

Detailed studies on target species to assess a generic product's equivalence with the innovator product are required. In addition, a dissolution profile should be provided. Chapter 13 explains how to document bioavailability and bioequivalence data.

Assessment of application dossiers for new or innovator products

Assessing dossiers for a new or innovator product (i.e., a product that has not previously been registered and marketed in the country), or a product for which the dosage form and route of administration is changing, should involve a comprehensive review and evaluation as described above.

Toxicological Studies. Toxicological studies are those performed by the innovator to assess product safety. This includes an examination and assessment of the study protocol, results, and conclusions regarding carcinogenicity, teratogenicity, and genotoxicity provided in the dossier.

Pharmacodynamic Studies. Pharmacodynamic studies are reviewed to assess the protocol, results, and conclusions from laboratory and clinical studies for establishing mode of action and secondary effects of the product as provided in the dossier.

Pharmacokinetic Studies in Humans and Animals. The protocol, results, and conclusions for absorption, distribution, metabolism, and elimination must be reviewed and assessed.

Clinical Studies (Studies on Target Species to Assess Efficacy and Safety). A description of the study protocol, results and conclusions for the clinical trials performed, benefits of the product, and the evidence of safety and efficacy provided in the dossier must be reviewed and assessed for correctness and completeness.

Proper and effective product dossier evaluation

The public generally expects to have access to all essential medicines they need and to receive new therapeutic advances without undue delay (Ericson et al., 2004). Those who evaluate a product dossier are advised to use a standard checklist developed by the national MRA along with standard specifications such as those used by the *United States Pharmacopeia*, *British Pharmacopoeia*, *International Pharmacopoeia*, *Pharmacopée Européenne*, *Martindale's Extra Pharmacopeia*, and other acceptable references. Evaluators are responsible for critically examining the accuracy, completeness, and originality of all documents, reports, and data provided; for example:

- Are documents printed on company letterhead, signed by authorized persons, and approved with official stamps or seals?
- Is information provided in the dossier meaningful, consistent, and logical?
- Are records complete, signed, and dated?
- Does product information in the dossier correspond to sample information, and contain no misleading information or claims?

Medicines evaluation committee

A medicines evaluation committee is part of an MRA and serves as an advisory body. For example, in Uganda, the Committee on National Formulary of the National Drug Authority is statutory, composed of scientific experts, and plays a decision-making role in product registration.[2] In Malaysia, a similar committee that consists of senior management and executives of all evaluation units is responsible for reviewing evaluation reports. Outside experts in various medical disciplines are appointed as reviewers for new drugs.

Competency of evaluators

The process of evaluating product dossiers for prescription and over-the-counter medicines requires personnel with appropriate qualifications, training, and scientific experience in disciplines such as pharmacy, pharmacology, microbiology, chemistry, biochemistry, toxicology, clinical trials, and other medical science disciplines.

Product dossiers should be reviewed by a committee or board that has official responsibility for conducting such a review. Committees are recommended to have the following types of representation:

- A senior clinician from a major teaching hospital
- A pharmacologist from a university or research institute or hospital
- Regulatory personnel from the national MRA
- A general or community practitioner
- A community pharmacist
- A manufacturing or GMP expert
- A pediatrician
- A representative from consumer associations.

Suspension or revocation of product registration

An MRA should have the power to remove deficient products from the market. In doing so, it may suspend or revoke registration or marketing authorization for a given product, if available information justifies such. Suspension can also occur if the product does not comply with MRA registration requirements, such as nonconformance with quality specifications, changes in product composition that are not approved by the MRA or if the MRA is not given proper and timely notification, or when manufacturing changes from a site that is GMP-compliant to a new site that does not comply with current GMP.

Assessing product application changes

An MRA is responsible for assessing requests to change registered products such as making variations to quality specifications, composition, packaging, manufacturing process or site of manufacture, and changes to the holder of marketing authorization. Applicants are usually charged a nominal fee for making such changes.

Changes may require resubmission of new samples, batch manufacturing records, stability studies reports, test procedures and specifications, certificates, licenses, and other information.

Renewal of product registration

Many countries authorize drug registration for limited periods of one to five years, after which a medicine must be re-registered or reauthorized. Applicants are also usually required to pay annual retention fees to keep their product on the market. MRAs are responsible for notifying applicants when their product registration is due for renewal.

Product renewals require a review and cross-check of market surveillance reports, product profiles, reports, histories of adverse drug events, punitive actions taken or pending against applicants, and any changes that have been made since the original product dossier was filed.

Inspection and Licensing Services

Inspection and licensing services involve inspection, licensing, and control of pharmaceutical manufacturing premises or establishments, importing and exporting agents, distributors, and wholesale and retail outlets of pharmaceutical products.

Inspection and licensing of pharmaceutical manufacturers

A manufacturing license, which is issued by an MRA, should be required for all medicines production. MRAs are advised to develop current GMP guidelines and procedures for inspecting pharmaceutical manufacturers. Guidelines should include clearly written instructions and checklists. Current GMP inspection reports should follow an agreed-upon format that follows WHO guidelines for pharmaceutical manufacturing inspection procedures. The acceptable minimum requirements for GMP compliance should be agreed on and followed by industry and government representatives alike.

Pharmaceutical manufacturers should be inspected before and regularly after licensing to ensure that their facilities and procedures comply with national and international current GMP guidelines. MRAs are advised to retain a master file of manufacturing premises. GMP inspectors should be qualified pharmacists, chemists, or other science graduates who possess practical experience in production and quality control of medicines, and should be experienced in current GMP and quality assurance.

MRAs in several resource-poor countries now conduct GMP inspections for local and foreign pharmaceutical manufacturers. Such inspections usually use a structured GMP/quality assurance inspection checklist that addresses all quality assurance measures taken during the manufacture, processing, packaging, and testing of products. Examples of these include the National Drug Authority in Uganda, the Food and Drug Administration of Tanzania, the Medicines Control Authority of Zimbabwe, and the National Agency for Food and Drug Administration and Control of Nigeria (www.nafdacnigeria.org).

Inspection and licensing of medicines distributors

All links in the distribution chain (importers, wholesalers, and retailers) require a license and they should be regularly monitored and inspected to ensure compliance with license conditions.

MRAs must ensure that all establishments that manufacture, import, export, store, distribute, and sell medicines are licensed. Activities and premises must comply with good distribution practice requirements.

Inspection enforcement units should be stationed at key entry points in the country, as well as in post offices, to detect and curb unregistered products from entering the country. Cambodia, Laos, and Vietnam, for example, train local health and pharmaceutical personnel to conduct inspections at ports of entry, wholesale premises, and retail pharmacies.[3] Inspections may involve examining product appearance, expiry date, packaging, package inserts, regis-

tration numbers, manufacturing licenses numbers, name and address of the manufacturer, and other labeling information.

Quality Assessment for Preapproval and Postmarketing Surveillance

Preapproval quality assessment

MRAs are advised to conduct appropriate screening and laboratory testing on samples before granting product registration to certify that products meet specifications for quality and conform to national registration requirements. In a resource-constrained setting, however, postmarketing surveillance may take priority over preapproval testing.

Postmarket surveillance

MRAs are advised to monitor the quality and safety of medicines to prevent harmful, substandard, and counterfeit medicines from reaching the public. A systematic surveillance program ensures that samples are randomly collected from the market and tested at scheduled intervals. Product labels and package inserts should be checked against those approved for registration. A system of product complaints regarding quality should also be instituted. Such complaints should be investigated and documented.

Product quality can be surveyed by analyzing samples taken from manufacturers and from the distribution chain—either randomly or when grounds exist to suspect that a product may be substandard or counterfeit. Tests should be performed to ensure conformance to compendia requirements (e.g., *British Pharmacopoeia*, *U.S. Pharmacopeia*, *International Pharmacopoeia*, etc.) or to the manufacturer's specifications where necessary.

Uganda's National Drug Authority, for example, carries out mandatory batch-by-batch laboratory analysis of all medicines intended to treat malaria and tuberculosis before they are cleared for entry into the country (http://www.nda.or.ug/).

Violations and punitive actions

Products that do not conform to required specifications for quality, safety, and efficacy may be recalled (if they have already entered the distribution system) or denied entry into the country and disposed of appropriately.

When violations are detected, MRAs are advised to institute punitive measures such as warnings; suspension or cancellation of product registration; license revocation for the wholesaler, retailer, or the local technical representative; or legal action.

Adverse Drug Reaction Monitoring

An adverse drug reaction (ADR) reporting system should be established to monitor medicine safety. MRAs are advised to establish an ADR advisory committee to review ADR reports. Networking with other international bodies and MRAs is a logical method for acquiring, sharing, and exchanging relevant information on medicine safety and for basing a decision on which to take appropriate action. Awareness programs to promote ADR reporting among medical and health professionals also should be conducted.

Disseminating Medicines Information

A systematic medicines information system should be established, including guidelines for ADR reporting and disseminating safety and quality information to practitioners, health professionals, consumers, and the general public via written publications, public announcements, and mass media.

When an MRA registers a product, a data sheet should be developed that contains indications for use, contraindications, and warnings. Such data sheets are the basis for preparing prescription and patient information. If there is a legal requirement that all commercial promotion of the product be consistent with the approved product information, the data sheet serves as a means of regulating the advertising and promotion of the product.

Implementing and Updating Medicines Regulations

Many countries do not regularly update their medicines legislation and regulations, or they may copy those of other countries, which do not reflect local realities.

The government branch that has responsibility for drug regulation must formulate new regulations or propose modifications to existing rules based on scientific and technological changes. Implementing or updating medicines regulation might include the following steps:

1. Stating the purpose of the regulation.
2. Defining categories of medicines and activities to be regulated.
3. Ensuring legal provision for the creation of an MRA.
4. Defining the roles, responsibilities, rights, and functions of all parties involved in the manufacture, trade, and use of medicines.
5. Setting qualifications and standards required for those who handle medicines.
6. Defining norms, standards, and specifications for assessing the quality, safety, and efficacy of medicines.
7. Developing relevant administrative tools—guidelines, forms, registers, certificates, standard operating procedures, lists, and logs.
8. Stating terms and conditions for suspending, revoking, or canceling pharmaceutical activities or practices and product licenses.
9. Defining prohibitions, offenses, penalties, and legal sanctions.
10. Creating mechanisms for ensuring transparency and accountability of the regulation.
11. Creating mechanisms for government oversight to assess medicines regulation implementation.

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[2] National Drug Policy and Authority Act, Chapter 206, Volume 6 of the Laws of Uganda. 1993.

[3] Information provided in 2003 by drug regulatory authorities of the Ministries of Health in Cambodia, Laos, and Vietnam.

Checklist 4.1
Establishing an effective medicines regulatory agency (MRA)

LEGISLATION, REGULATION, AND POLICY

- ☐ Establish a medicines law:
  - To control medicine production, importation and exportation, sale, distribution and use.
  - To provide clear and specific provisions regarding sanctions and punitions.
- ☐ Enforce laws.
  - Ensure compliance with the law by all practitioners of medicine production, importation, exportation, sale, distribution, and use.
  - Authorize the MRA to take punitive actions against violations.
- ☐ Establish regulations governing specific medicine activities.
- ☐ Establish a national medicinal drug policy to include:
  - Equitable access to essential medicines
  - Quality, safety, and efficacy of medicines
  - Rational use of medicines
  - Viable, local pharmaceutical industry.

GENERAL REGULATORY ASPECTS

- ☐ Authorize the MRA:
  - To oversee product assessment, and to authorize medicine registration and marketing activities
  - To inspect and license pharmaceutical establishments, and to control production, importation, and exportation
  - To establish a quality control laboratory
  - To perform postmarketing surveillance for quality and adverse drug reactions
  - To control drug promotion and advertisement activities
- ☐ Promote effective cooperation between MRA and other law enforcement agencies, including:
  - Customs
  - Police
  - Local authorities.

PERSONNEL AND FINANCIAL RESOURCES

- At least two pharmacists to perform product assessment and registration, and marketing authorization.
- At least four pharmacists to inspect and license pharmaceutical establishments, and to control production, importation, and exportation.
- Quality control laboratory (medium-size) staff requirements: 4–5 analysts, 6–8 laboratory technicians, and 2–4 supporting and housekeeping staff. The ratio of the analysts to laboratory technicians must be relatively high in a laboratory that analyzes a range of pharmaceutical products (World Health Organization, 1997a). The ratio may

be smaller in laboratories that perform repetitive testing of batches of a limited number of products.

- Analysts may be chemists, pharmacists, or microbiologists.
- One pharmacist and one clinician or physician authorized to perform postmarketing surveillance and product recall.
- One pharmacist, pharmacologist, or physician authorized to oversee drug promotion and advertisement.
- Adequate financial resources must be available to carry out key functions, sustain performance, and support personnel in their career development and growth.

TECHNICAL ELEMENTS

- Simplified and validated testing methods for basic testing must exist.
- Quality specifications of active pharmaceutical ingredients and finished products must exist.
- National or WHO good manufacturing practice guidelines must be followed.
- Good laboratory practice guidelines must be followed.
- Good storage practices must be established and followed.
- Good pharmacy or dispensing practices must be established and followed.

☐ Product assessment and registration:

- Establish a manual or computerized system for product assessment and registration.
- Assess products on the basis of safety, quality, efficacy, accuracy, and completeness of packaging information.
- Use or participate in a WHO certification scheme for product quality, safety, and efficacy information.
- Allow interchangeability of data for generic products.
- Review legal status of products in other countries.
- Establish technical cooperation or collaboration with other MRAs to exchange information on safety, quality, efficacy, and trust of packaging.

☐ Inspection, licensing of pharmaceutical establishments, and control of production, importation and exportation:

- Perform routine and necessary inspections.
- Enforce compliance with good manufacturing practices, good laboratory practices, good dispensing practices, and good storage practices.
- Apply standard operating procedures and perform GMP inspections.
- Install drug inspectors at ports of entry who can physically examine all medicine imports before medicines are approved for entry into the country.

☐ Quality control laboratory:

- Establish an MRA laboratory that is capable of performing tests of active pharmaceutical ingredients and finished drug products to verify their identity, perform an assay for

contents of active pharmaceutical ingredients and dissolution for most essential medicines sold in the country (see Laboratory Testing, chapter 8).

- ☐ Postmarketing surveillance and product recall:
  - ☐ Establish a monitoring and reporting mechanism for quality, adverse drug reactions, and product recalls.
- ☐ Control of drug promotion and advertisement:
  - ☐ Establish and apply guidelines consistent with WHO Ethical Criteria for Medicinal Drug Promotion (World Health Organization, 1988).
  - ☐ Establish a prior approval process for advertising and promotional materials.

CHAPTER 5

Establishing Medicines Quality Through Good Manufacturing Practice

This chapter explains the concept of good manufacturing practice (GMP) and offers guidance for establishing a system to ensure the availability of high-quality medicines in resource-limited settings by meeting GMP requirements.

The pharmaceutical industry is responsible for ensuring that manufactured medicines are safe, effective, and of good quality. To survive in an increasingly competitive global marketplace, the industry must invest in technology to produce quality products to meet standards of excellence. Assuring high-quality pharmaceutical products is a business goal, one required by regulation to achieve. Thus, regulatory authorities require that medicines are produced and packaged according to current GMP in an effort to protect the public from potential health hazards of substandard products.

A checklist for ensuring medicines quality through GMP appears at the end of the chapter (Checklist 5.1).

What Is GMP?

GMP is that part of quality assurance that ensures that medicinal products are consistently produced and controlled according to the quality standards of their intended use and product specifications.

Many countries have their own GMP guidelines, and manufacturers must be familiar with the regulatory requirements in countries where they intend to manufacture their products. Basic GMP principles are well specified by the World Health Organization (2000a) and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.[4] Most resource-limited countries have adopted the WHO

GMPs as national standards. These guidelines provide a basis for drug manufacturers to develop their own detailed GMP guidelines.

These are the objectives of GMP:

- To ensure that all manufacturing processes are clearly defined, systematically reviewed on the basis of experience, and shown to be capable of consistently manufacturing quality pharmaceutical products to comply with established specifications.
- To ensure that qualification and validation are performed. Qualification means a condition or standard that must comply with standard GMP requirements for facilities, equipment, and personnel. Validation means conforming to accepted and valid principles and methods regarding manufacturing plans and records, equipment, utilities, facilities, and processes.
- To ensure that all necessary resources are provided, including qualified and trained personnel; adequate premises and space; suitable equipment and services; appropriate materials, containers, and labels; approved procedures and instructions; suitable storage and transport; and adequate laboratories and equipment for in-process control.
- To ensure that procedures are written clearly.
- To ensure that equipment operators are trained to adequately carry out procedures.
- To ensure that adequate manufacturing records are retained—manually or with recording instruments—to prove that the quantity and quality of the product meet expectations, and that any significant deviations are fully recorded and investigated.
- To ensure that manufacturing and distribution activities are recorded and accessible to provide a complete history of a batch; a system should be in place to recall any batch of product at any time,
- To ensure that product complaints are examined, quality defects are investigated, and appropriate measures are taken.

Meeting GMP Requirements

The establishment and implementation of an effective quality assurance program is an essential part of any drug manufacturing process.[5] Medicine manufacturers often have a department that is fully dedicated to addressing quality-related matters. It is most often independent of other departments, including the production department, and is staffed with well-trained personnel. Medicine manufacturers should have an efficient and comprehensive quality unit. Inevitably, this means making available adequate resources to support various quality assurance tasks.

Figure 5.1 contains a schematic presentation of the interrelationship among quality control, GMP, and quality assurance. Many of the activities associated with GMP may require laboratory staff with expertise in chromatographic or spectrometric analysis.

The main responsibility of a manufacturer's quality control or quality assurance department is to ensure that manufacturing processes comply with GMP requirements. The tasks of a manufacturer's quality department are many and varied, for example:

- Determining the specifications of raw materials, packaging, and products.

- Ensuring raw materials are properly received, quarantined, stored, and released.
- Collecting and analyzing samples.
- Inspecting manufacturing facilities and processes.
- Verifying computer systems.
- Organizing stability tests.
- Releasing a drug to market.
- Managing complaints and recalls.
- Developing and maintaining the documentation system.
- Conducting regular internal audits and inspections.
- Training employees on GMP requirements.
- Acting as liaison between manufacturer and regulatory authorities.

For a detailed list of the responsibilities of a quality unit, see World Health Organization (2000a).

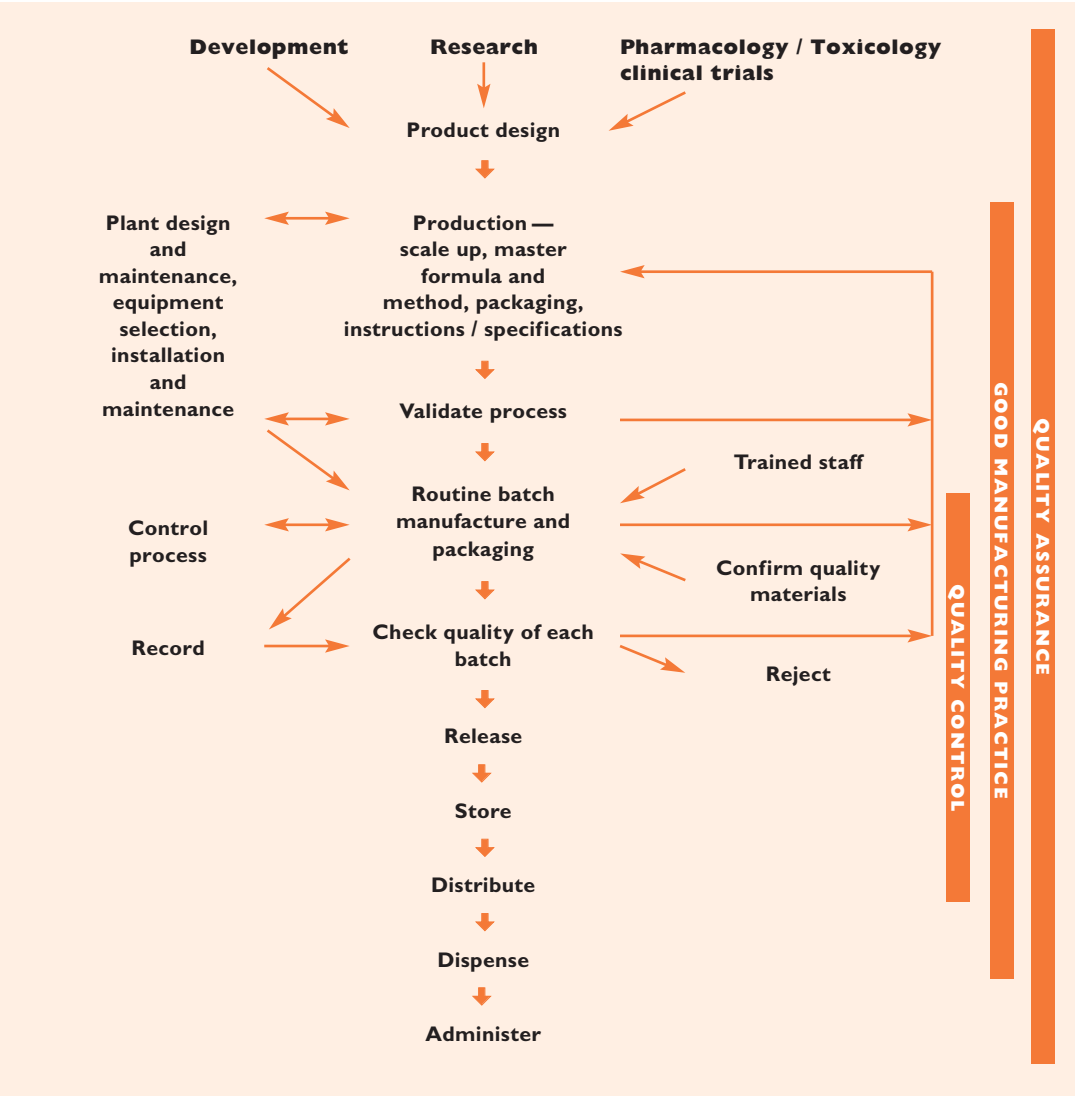

Figure 5.1 Quality assurance and good manufacturing practices

Source: J. Sharp. *Quality Manufacture of Medicines and Other Healthcare Products*. London, UK: Pharmaceutical Press; 2000.

Complying with GMP in resource-limited countries

Local medicine manufacturers in settings with limited resources usually operate under difficult conditions and with tight budgets. Organizing and implementing a quality unit is a significant financial, logistical, and organizational undertaking. Pharmaceutical manufacturers, despite operating within resource-limited environments, must adhere to basic GMP principles, even if their focus is on meeting the needs of the local market. Of particular danger is the high prevalence of infectious diseases, which if treated with substandard medicines, may introduce resistance that could have dire consequences for both local and global public health. This in itself should be reason enough to encourage and enforce adherence to quality standards.

Many leading nongovernmental and international organizations (e.g., the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria; the World Bank; UNICEF; and the Global TB Drug Facility) that procure pharmaceuticals now require their products can be procured only from internationally recognized GMP-compliant suppliers (United Nations Development Programme, 2005). From an economic and viability point of view, manufacturers must embrace GMP principles. Some manufacturers in resource-limited countries already produce drugs at the highest standards of quality, which proves the ability to manufacture under current GMP guidelines. Often, attention to simple procedures is all that is required for a manufacturer to meet GMP compliance.

This is certainly true for small drug manufacturing operations. For example, manufacturers should make sure that the buildings used to produce medicines are clean and protected from outside elements (wind, dust, temperature extremes). Producers should validate the identification and purity of active pharmaceutical ingredients before using them. Standard operating procedures on all basic and critical processes in manufacturing should be drafted and implemented; clearly written instructions that are easily understood by employees are preferred to complex procedures that may be difficult to interpret and implement. The WHO GMP guidelines specify which manufacturing activities require standard operating procedures (World Health Organization, 2000a).

GMP benefits

To ensure product quality and patient safety, drug manufacturers often go beyond complying with basic GMP principles resulting in:

- Assurances of patient safety and welfare
- Greater confidence in products
- Competent production, handling, and distribution, which leads to cost savings, improvement in efficiency, and an increase in profitability
- Prevention, identification, and resolution of quality problems in a timely manner
- Greater manufacturing consistency and better product quality
- Fewer barriers to global markets.

Obstacles to GMP compliance

Although major efforts have been made in some resource-limited countries to develop operational medicine regulatory authorities, weak regulations still exist. Without a strong regulatory policy, manufacturers may not feel obligated to produce high-quality pharmaceutical products.

If a medicines regulatory policy is well established, drug manufacturers may face costly product licensing and registration. For example, regulators require manufacturers to provide bioavailability/bioequivalence (BA/BE) study results. Through cooperation with multinational organizations, such as the World Health Organization, simplified screening protocols can be developed to provide specific guidance to manufacturers and drug regulatory authorities regarding bioavailability testing and drug registration requirements. (Chapter 13 discusses bioavailability and bioequivalence studies.)

Some large pharmaceutical companies have subsidiaries in resource-limited countries, but most such manufacturing activities are relatively small operations that add value to imported active ingredients to produce essential generic medicines. Local pharmaceutical manufacturers might have a limited number of employees. Small operations, such as hospital-based manufacturing sites that produce fluids, for example, will not require a large quality assurance department, but their small-scale nature does not justify eliminating the need to manufacture according to accepted quality standards. The manufacturer should ensure that critical steps in the manufacturing operation are performed in accordance with domestically or internationally accepted standards of current GMP. The manufacturing process is a cascade of processes that are critical to the quality of the end product. Identifying these critical points is an important step in meeting GMP (for additional information, see World Health Organization, 2003a).

Additional reasons for not being able to conform to GMP might include:

- Weak national drug regulations
- Absence of quality assurance technical expertise at the national level
- Pharmaceutical company management not committed to quality assurance and GMP
- Expense of setting up a quality assurance system
- Lack of skilled quality assurance personnel in the manufacturing process
- Social and cultural perceptions
- Public not educated about the dangers of using substandard medicinal products.

Strengthening medicines quality/GMP compliance

Sensitizing governments, the public, and drug manufacturers to the benefits of producing good-quality medicines is not an easy undertaking and requires a partnership among all key players: the public, national governments, domestic medicine manufacturers, and multilateral organizations. The following options can help promote compliance with quality standards in resources-limited settings:

- Countries are advised to assess the present state of GMP compliance by conducting a comprehensive GMP inspection to identify weaknesses, strengths, and gaps.
- Countries are encouraged to adopt a GMP standard where one is lacking, or to conform to international standards. Nations are advised to consider passing legislation that makes GMP compliance mandatory.
- Countries are advised to obtain support from other countries or multinational organizations with GMP experience via bilateral or multilateral agreements and other geopolitical considerations.
- Medicine regulatory authorities are advised to monitor GMP at manufacturing sites.

- Medicine manufacturers should be encouraged to set up a quality assurance system by stressing its advantages to management and employees. GMP principles are not an impediment to manufacturing, but principles based on sound scientific judgment, which if followed, make good business sense.
- Medicine manufacturers are advised to be aware of GMP inspections by regulatory agencies and the consequences of noncompliance. Regulatory authorities might consider developing channels through which this information is disseminated to manufacturers on a regular basis.
- Medicine manufacturers are advised to pursue and obtain quality certification (the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce). However, regulatory authorities should have a mechanism in place to ensure that manufacturers do not misuse the certification. A model certificate of a pharmaceutical product is appended to this chapter as Form 5.1.
- Communication between MRAs and manufacturers should be promoted through regular meetings. A newsletter is a useful channel through which dialogue can occur between regulatory authorities and manufacturers.
- Decisions made by a medicines regulatory authority with justification (e.g., recall, withdrawal, revocation of registration and licenses, etc.) should be made public.
- Punitive measures should be in place for manufacturers that do not conform to GMP. Procurement agencies and hospitals should be required to purchase drugs from only GMP-conforming manufacturers.
- Countries and large multinational companies should explore ways of creating an environment in which appropriate technology, human, equipment, and technical know-how might be transferred to local subsidiaries in resource-limited countries.
- Quality assurance personnel associated with the national regulatory authority and the manufacturer should participate in regular GMP training.
- Regulators, manufacturers, and other interested parties in low-income countries should be involved in international decisions regarding quality. This gives countries the opportunity to articulate and defend specific needs that might be unique to their domestic or regional situation.
- Quality assurance inspections should be conducted in a cost-effective manner, and an independent third-party laboratory should conduct the quality analysis.
- GMP training modules can be incorporated into undergraduate or paramedical courses.
- The public can be educated and empowered to make informed decisions. Radio programs or health care volunteers can sensitize communities about the potential health risks of substandard medicines.
- The formation of regional professional bodies that promote quality assurance systems should be encouraged.

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[4] ICH Q7A—Good manufacturing practice for active pharmaceutical ingredients, 10 November 2000. Also available online from the official ICH web site: http://www.ich.org.

[5] In the European Union, for example, EC directives 91/356/EEC and 91/412/EEC explicitly state the need for a QA program.

Checklist 5.1
Building medicines quality through good manufacturing practices

For an MRA:

LEGISLATION, REGULATIONS, AND POLICY

- ☐ Devise national legislation and regulations for controlling pharmaceutical production.
- ☐ Establish current good manufacturing practice guidelines.
- ☐ Establish compliance with current GMP guidelines for medicine production by law or regulation.
- ☐ Enforce GMP adherence by all medicine manufacturers.

For Manufacturers:

OPERATIONS AND PRACTICES

- ☐ Establish a quality assurance department or unit to perform routine internal GMP audits.
- ☐ Establish quality assurance functions:
  - ☐ Check and clear all incoming raw pharmaceutical materials, including inert pharmaceutical substances, active pharmaceutical ingredients, and packaging and labeling materials.
  - ☐ Write and approve standard operating procedures, and validate testing methods, equipment, and production process.
  - ☐ Conduct in-process control activities, including testing for quality of all materials to be used in manufacturing before their use, and semifinished- and finished-product testing.
  - ☐ Approve batch or lot release.

PERSONNEL AND QUALIFICATIONS

- ☐ Establish adequate professional knowledge, experience, and technical skills:
  - ☐ Include at least one pharmacist in charge of manufacturing each dosage form production unit.
  - ☐ Employ at least two responsible pharmacists who oversee quality assurance and quality control in small-scale manufacturing plants.
  - ☐ Employ at least two responsible pharmacists or chemists in quality control laboratories.
  - ☐ Write a job description for each position.
  - ☐ Participate in each current standard operating procedures and batch record training.
  - ☐ Attend to current GMP regulations and guidelines.
  - ☐ Assign a qualified person to specific equipment or production processes.
  - ☐ Establish a training record for each individual.
  - ☐ Periodically review each individual's performance.

TECHNOLOGY AND EQUIPMENT

- ☐ Use appropriate technology and equipment to manufacture medicinal drug preparations.
- ☐ Maintain manufacturing and quality control equipment according to current standards and reliable performance.

- ☐ Apply validation protocols to address accuracy, precision, specificity, and detection and quantification limits for contaminants.
- ☐ Ensure that validation protocols address:
  - ☐ Calibration, use, cleaning, and maintenance of equipment
  - ☐ Installation of unique equipment identification, establishment of a log book, fulfillment of utility requirements at the specified site
  - ☐ Performance qualification to verify that processed materials meet acceptance criteria
  - ☐ Cleaning validation to ensure
    - ☐ Proper cleaning
    - ☐ No risk of cross-contamination
    - ☐ Cleanliness testing based on acceptance criteria
    - ☐ Use of acceptable quality water or cleaning liquid
- ☐ Validate utilities
  - ☐ Purified water
    - ☐ Water source is routinely sampled and tested for compliance with regulatory requirements.
    - ☐ Major contaminant groups (particulates, inorganics, organics, and microbes) are removed.
    - ☐ Samples are collected weekly at sampling points and point-of-use ports, and tested for quality based on acceptance criteria.
    - ☐ Test data records for trends are maintained.
- ☐ Validate facility
  - ☐ Verify facility design to ensure:
    - ☐ No mix-up or cross-contamination
    - ☐ Sufficient space for operation and maintenance of equipment
    - ☐ Facility cleanliness
  - ☐ Verify construction to ensure:
    - ☐ As-built drawings conform to design drawings.
    - ☐ Construction materials are as specified.
    - ☐ Equipment has been installed as planned.
    - ☐ Utilities are routed as planned.
  - ☐ Verify operation and performance to ensure:
    - ☐ The facility can support the manufacturing process.
    - ☐ The facility meets cleanliness specifications.
    - ☐ Production of three successful consecutive batches using qualified materials, validated equipment and utilities, and methods should be validated.

MULTIPRODUCT FACILITY

- ☐ Ensure validated procedures exist for product turnover:
  - ☐ Equipment cleaning
  - ☐ Facility cleaning

DOCUMENTATION

- ☐ Establish a documentation system such as commitment documents, directive documents, data collection records, and reports.
- ☐ Establish an inventory list of all documents.
- ☐ Review manufacturing and control documents to ensure:
  - ☐ Lot/batch of raw materials can be traced.
  - ☐ Equipment used in manufacture can be identified.
  - ☐ Work performed by an assigned person can be identified.
  - ☐ All calculations are checked.
  - ☐ All labels are correct.
  - ☐ Quality control record is complete.

Form 5.1
WHO Certification Scheme: Model Certificate of a Pharmaceutical Product

This certificate conforms to the format recommended by the World Health Organization.[1]

No. of Certificate:

Exporting (certifying) country:

Importing (requesting) country:

Name and dosage form of product:

Active ingredient(s)[2] and amount(s) per unit dose.[3]

For complete composition, including excipients see attached.[4]

1.2 Is this product licensed to be placed on the market for use in the exporting country?[5]
☐ Yes ☐ No (key in as appropriate)

1.3 Is this product actually on the market in the exporting country?
yes/no/unknown (key in as appropriate)

If the answer to 1.2 is Yes, continue with section 2A and omit section 2B.z

If the answer to 1.2 is No, omit section 2A and continue with section 2B.[6]

2A.1 Number of product license[7] and date of issue:

2A.2 Product-license holder (name and address):

2A.3 Status of product license holder[8]: a/ b/ c/ (indicate appropriate category; see note 8)

2A.3.1 For categories (b) and (c) indicate the name and address of the manufacturer producing the dosage form [9]:

2A.4 Is summary basis of approval appended?[10] yes/no (key in as appropriate)

2A.5 Is the attached, officially approved product information complete and consonant with the license?[11] ☐ Yes ☐ No ☐ Not provided (key in as appropriate)

2A.6 Applicant for certificate, if different from license holder (name and address)[12]:

2B.1 Applicant for certificate (name and address):

2B.2 Status of applicant: ☐ a ☐ b ☐ c
(key in appropriate category as defined in note 8)

2B.2.1 For categories (b) and (c) the name and address of the manufacturer producing the dosage form is[9]:

2B.3 Why is marketing authorization lacking?
☐ not required ☐ not requested ☐ under consideration ☐ refused
(key in as appropriate)

2B.4 Remarks[13]:

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?
☐ Yes ☐ No ☐ Not applicable[14] (key in as appropriate)

If no, or not applicable proceed to Question 4.

3.1 Periodicity of routine inspections (years):

3.2 Has the manufacture of this type of dosage form been inspected?
☐ Yes ☐ No (key in as appropriate)

3.3. Do the facilities and operations conform to GMP as recommended by the World Health Organization?[15] ☐ Yes ☐ No ☐ Not applicable[14] (key in as appropriate)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product.[16]
☐ Yes ☐ No (key in as appropriate)

If no, explain:

Address of certifying authority:

Telephone No.: Fax No.:

Name of authorized person:

Signature:

Stamp and date:

General instructions for Model Certificate of a Pharmaceutical Product

Please refer to the guidelines for full instructions for completing this form and information on the implementation of the Scheme.

The forms are suitable for generation by computer. They should always be submitted on paper, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes for Model Certificate of a Pharmaceutical Product

[1] This certificate, which is in the format recommended by the World Health Organization, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. Use one form for each product, because manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

[2] Whenever possible, use International Nonproprietary Names or national nonproprietary names.

[3] The formula (complete composition) of the dosage form should be given on the certificate or be appended.

[4] Details of quantitative composition are preferred, but their provision is subject to the agreement of the product's license holder.

[5] When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is specified in the product license.

[6] Sections 2A and 2B are mutually exclusive.

[7] Indicate, when applicable, whether the license is provisional or if the product has not been approved.

[8] Specify whether the person responsible for placing the product on the market:

(a) Manufactures the dosage form;

(b) Packages or labels a dosage form manufactured by an independent company; or

(c) Is involved in none of the above.

[9] This information can be provided only with the consent of the product license holder or, for nonregistered products, the applicant. If this section is not completed it indicates that the party concerned has not agreed to inclusion of this information. Note that information concerning the site of production is part of the product license. If the production site is changed, the license must be updated or it is no longer valid.

[10] This refers to a document prepared by national regulatory authorities that summarizes the technical basis on which the product has been licensed.

[11] This refers to product information approved by the competent national regulatory authority, such as summary product characteristics.

[12] In this circumstance, permission for issuing the certificate is required from the product license holder. This permission has to be provided to the authority by the applicant.

[13] Please indicate the reason the applicant has provided for not requesting registration:

(a) The product has been developed exclusively for the treatment of conditions—particularly tropical diseases—not endemic in the country of export;

(b) The product has been reformulated with a view to improving its stability under tropical conditions;

(c) The product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;

(d) The product has been reformulated to meet a different maximum dosage limit for an active ingredient;

(e) Any other reason, please specify.

[14] Not applicable means that manufacture is taking place in a country other than that issuing the product certificate, and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the 32nd report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

[16] This section is to be completed when the product license holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances, the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

This Model Certificate is available on the WHO/EDM website at: www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifscheme.shtml.

CHAPTER 6

Ensuring Medicines Quality Through Procurement

Procurement plays an important role in ensuring that quality medicines are supplied to the health care system. The purpose of this chapter is to review the objectives of a procurement system; depict the resources required to operate and maintain an effective procurement system; and describe the procurement process and key activities, procedures, and documents that a procurement office should use to obtain good quality products.

In many countries, the procurement of essential medicines is carried out by different programs and organizations using different methods and quality standards, with little efficient coordination, which leads to inefficiencies and waste. If it is not possible to combine all procurement within a country, national government organizations are advised at least to follow the information outlined in this chapter.

A government may choose from several procurement options to obtain medicines that meet its national requirements. The most common method is to establish a designated procurement unit as part of the Ministry of Health. That unit takes full responsibility for procuring national drug and medical supplies in accordance with national, and, if applicable, donor procurement regulations.

A checklist for establishing an effective procurement unit appears at the end of the chapter (Checklist 6.1).

Procurement System Objectives

An effective and efficient procurement system is designed to obtain the correct medicines and products of good quality, at the right time, in the required quantities, and at favorable cost.

To successfully achieve these objectives, a procurement unit must work closely with other personnel in the product management cycle—supplier, distributor, customer. The procure-

ment office bears significant responsibility for ensuring that quality assurance measures are incorporated and enforced so that only acceptable medicines and products are available for distribution and use.

A procurement system needs appropriate and adequate resources to achieve its objectives.

Human resources. Human resources are experienced staff, including management, who are qualified and trained in procurement procedures, logistics, international trade, and financing, and who have no conflicts of interest.

Financial resources. An adequate budget is needed to hire and retain competent staff and provide necessary operational resources.

Operational resources. Adequate office space and proper equipment to maintain operations are required, as is current information about suppliers and products.

System resources. System resources include a written procurement policy that identifies a transparent solicitation process that is open to public review and scrutiny, and evaluation procedures, documentation requirements, and government procurement regulations.

The Procurement Process: Ensuring Quality Medicines

The procurement process is a series of activities designed to obtain good-quality medicines at the right time, in the right quantities, and at favorable costs (Figure 6.1). While there is some variation in the process, depending on the bidding method chosen and whether prequalification or postqualification of suppliers occurs, the basic activities in the process are these:

- Determine requirements; select and quantify products.
- Prepare technical specifications.
- Select suppliers.
- Prepare bid documents.
- Release bid documents.
- Receive and evaluate offers.
- Award a contract.
- Inspect products and test for quality, if necessary.
- Monitor supplier performance and product quality.

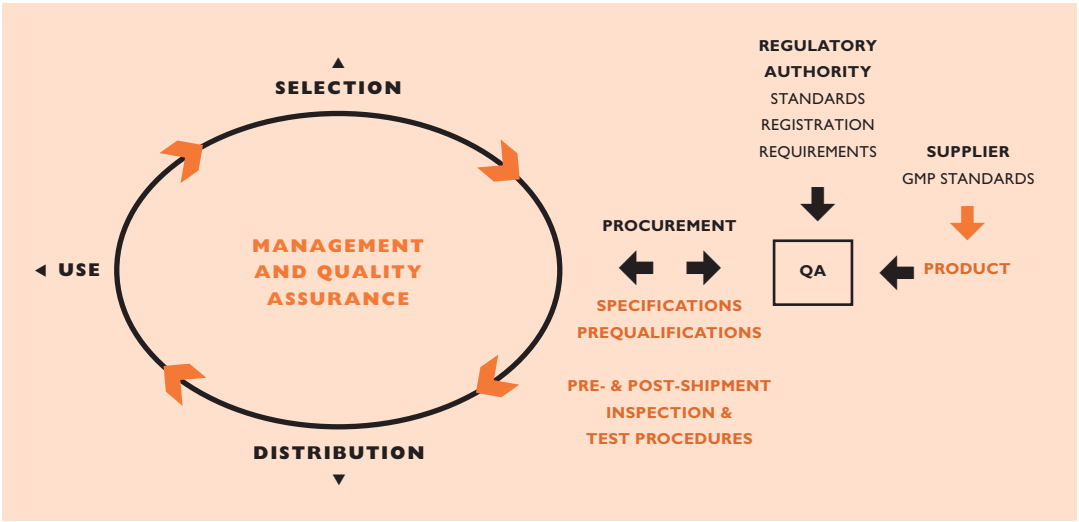
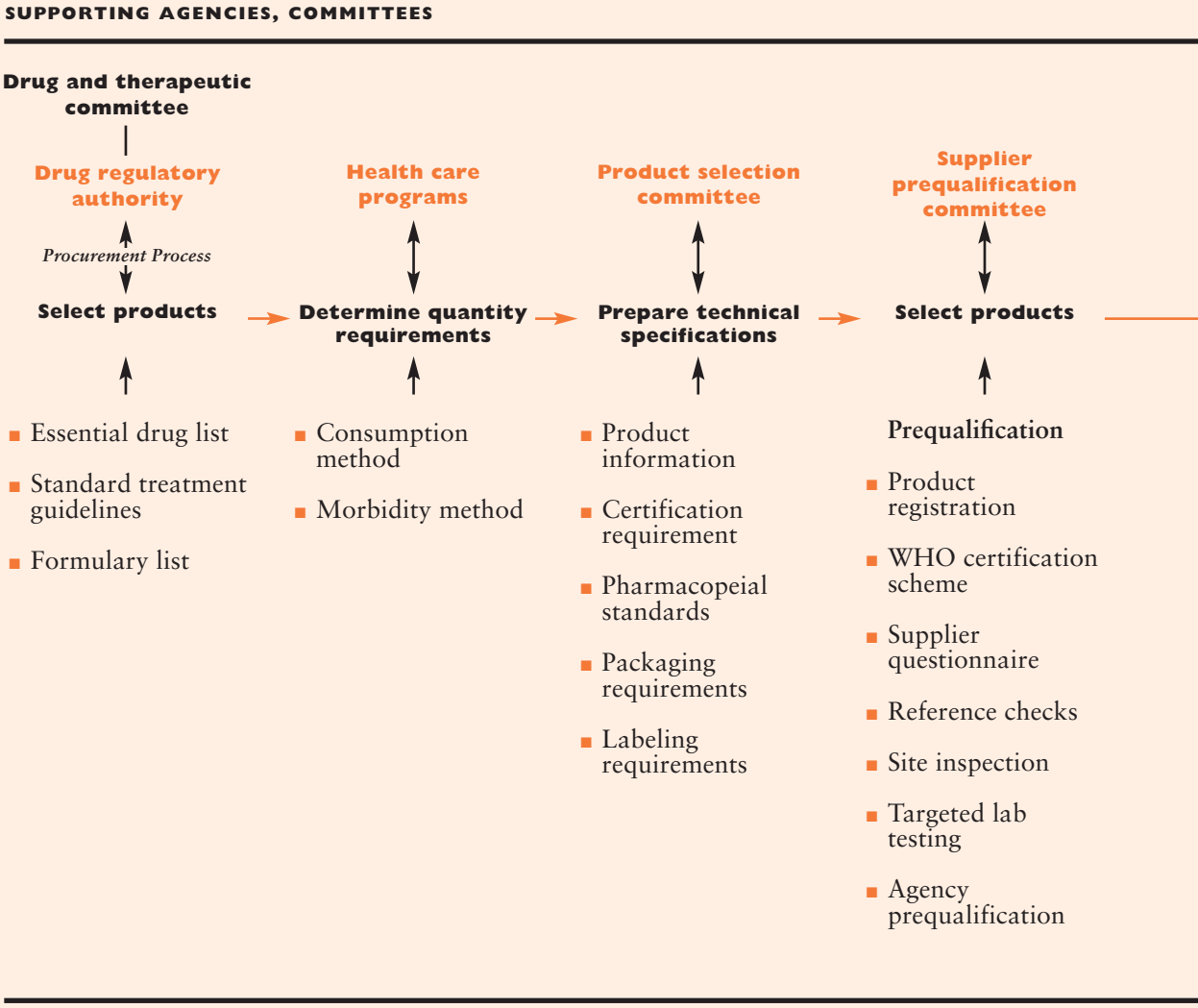


Figure 6.1
Product management cycle

Source: *The Logistics Handbook: A practical guide for supply chain managers in family planning and health programs*. Arlington, VA: John Snow, 2000.

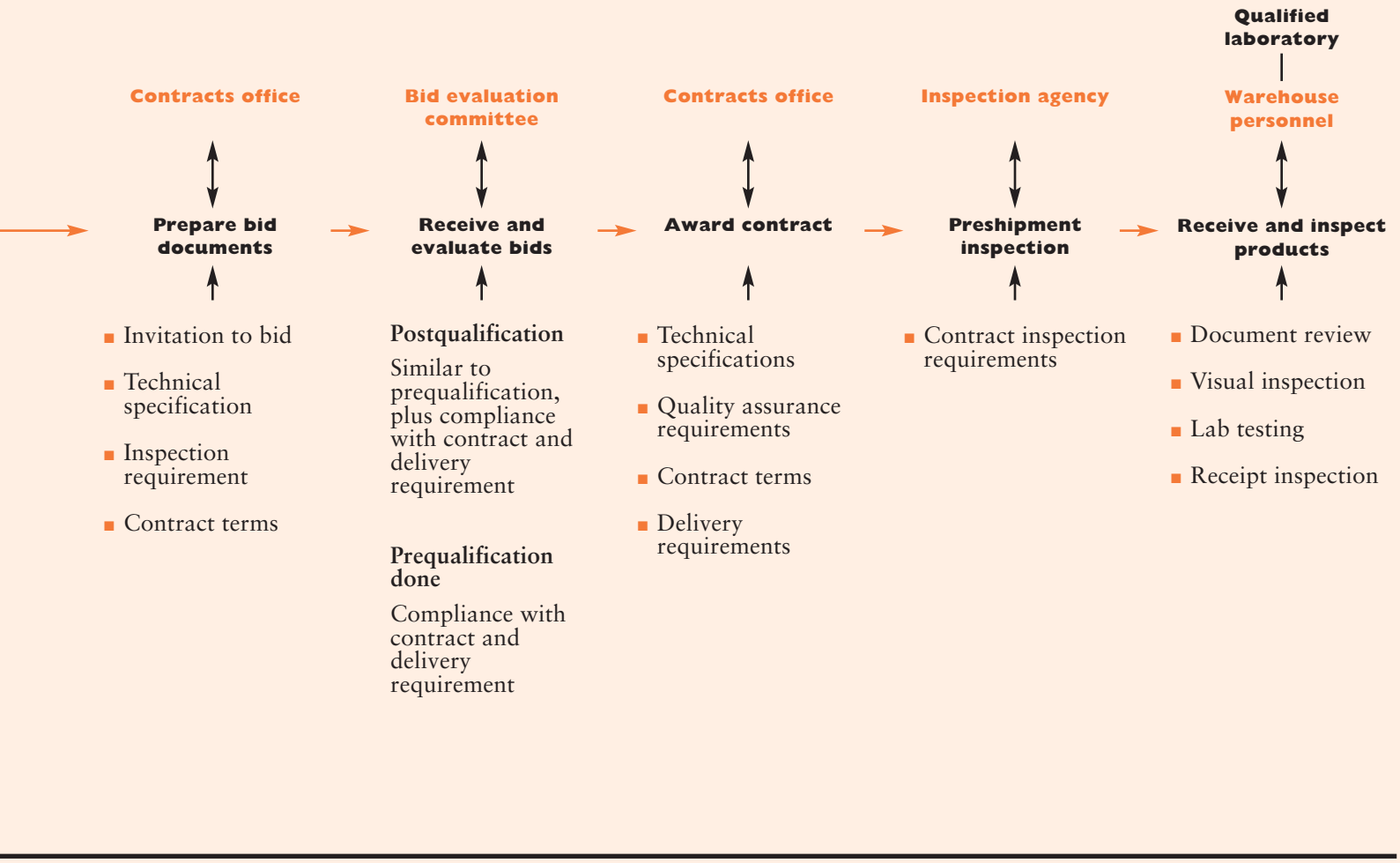
Figure 6.2
Quality assurance in the medicines procurement process



While the sequence of activities presented in the list above reflects the traditional procurement process, conducting several of the activities at the same time is the most common process. Other activities can be performed separately, but within the same time frame. For example, Ministry of Health program staff can determine the quantity of medicines needed, while technical staff can develop procurement technical specifications.

Additionally, program staff might select and quantify medicines at the same time, culminating in a list of specifications and required quantities. Or, procurement staff may generate a list of prequalified suppliers allowed to participate in the bidding process, while contract officers prepare bid documents and the text of the purchase contract.

In an effective procurement system, several of these activities are often handled by separate groups (individuals, committees, subcommittees), and the procurement office is responsible for coordinating the technical information and expertise each group provides. A schematic summary of quality assurance in a procurement process is shown in Figure 6.2.



Determine requirements

Two important first steps in the procurement process are:

1. Select the medicines to be procured.
2. Determine the required quantity of each medicine and its approximate total value.

SELECT MEDICINES

A selection committee must obtain information from the appropriate national agency about which medicines or products to order. How this information is obtained differs from country to country, depending on whether a national medicines policy, supported by a functional medicines regulatory authority (MRA), is in place.

A medicines regulatory authority is present. In countries that have an effective national policy, the medicines regulatory authority implements and enforces most of the regulations regarding pharmaceutical products. Its primary responsibility is to ensure the quality, safety,

and efficacy of locally manufactured and imported pharmaceuticals and medicines.[6] An effective national drug policy will usually result in the development of an essential medicines list (EML) that satisfies the health care needs of the majority of the population. In countries that have established an EML, selecting products for national health care programs should be limited to products that have been registered by the medicines regulatory authority and appear on the list.

If a functional national medicines selection committee or formulary committee exists, that group is advised to screen the list of products submitted to the procurement office to ensure they are registered with the MRA and appear on the EML. In countries where such a committee does not exist, the procurement office is advised to work with the MRA to establish an information exchange system that allows the office to learn whether requested products have been officially registered with the MRA.

Medicines that are not yet registered, but appear on the EML, could also be admitted to the procurement system, however, on the condition that they will be registered once a purchase contract has been granted.

Product (i.e., medicines) registration is independent of the procurement process and can occur any time in the procurement process. However, a medicine must eventually be registered by the MRA before its release for long-term program use.

A medicines regulatory authority is not present. If an MRA has not been established, or if it operates with limited capacity to evaluate pharmaceutical products, the procurement office must turn to other sources to identify the correct products to order.

One source of information at the national level may be the EML, which may exist even in countries that do not have a functional MRA. The procurement office is responsible for reviewing the EML to confirm that the medicines being requested appear on the list.

Another source of information can be standard treatment guidelines, generally developed for hospitals, or for regional or national use, and for disease control programs. While these guidelines help practitioners determine appropriate treatments, they also identify the medicines recommended for treatment, which in most cases, are selected from the EML.

Most hospitals and some national governments have medicines and therapeutic committees that can serve as a resource in selecting appropriate products. The members of these committees generally have pharmaceutical and medical expertise and are responsible for developing policies and procedures for the rational selection, procurement, and use of pharmaceutical products and medicines.

A formulary list and manual—medicines and therapeutic products approved for use in a specific health care setting—can be created for national, regional, or hospital use. A formulary manual contains summary medicine information or regimens for individual medicines.

Whether or not a functional national medicines regulatory agency exists, the procurement office must proactively seek out the appropriate resources and technical expertise to confirm that acceptable products are being requested. The procurement office must also be prepared to respond to special requests for new medicines by identifying the appropriate technical resource capable of validating and authorizing the request.

ESTABLISH PRODUCT QUANTITY

Traditionally, a nation's health care program staff identifies the quantities of medicines the country needs. The process for quantifying product requirements varies from country to country, but the two most common methods are the consumption method, which uses data based on current medicine use, and the morbidity method, which forecasts the anticipated quantity of medicines needed to treat an expected number of cases of specific diseases based on incidence data.

The procurement office assembles quantity requirements from various sources into a final estimate of total medicine requirements. The procurement office contacts all potential program managers to ensure no disease program is overlooked. The procurement office also advises program managers of the estimated procurement lead time (i.e., the time from receiving requests to medicine delivery) to ensure that requirements are submitted and received in a timely manner. The procurement office then organizes medicine requirements into the largest possible quantities to achieve favorable prices and contract terms from suppliers.

Medicines should be identified by their International Nonproprietary Name (INN) or generic name, the strength of each component, the basic unit and package size, and total number of packages required (Management Sciences for Health, 1997). Use of the INN avoids purchase of more expensive brand-name products.

Prepare technical specifications

Technical specifications identify the requirements with which a supplier must comply and the related supporting documentation that a supplier must provide. Establishing a clear, well-defined technical specification is one of the key steps in ensuring that quality medicines will be procured and delivered.

Technical specifications are often prepared by a procurement office, which works closely with a medicines selection committee that provides technical expertise about the specific medicines being requested.

Technical specifications for pharmaceutical products and medicines will typically include the following:

- Product information requirements
- Certification requirements
- Pharmacopeial standards
- Labeling requirements
- Packaging requirements
- Other evidence of product quality pertinent to the specific products being requested.

PRODUCT INFORMATION REQUIREMENTS

Product or medicine information requirements include data on active ingredients, dosage forms, finished product specifications, pharmacology, stability test data, and other pertinent information. If suppliers have been prequalified,[7] most of this information will already have been obtained and evaluated.

The procurement office must cooperate with technical personnel to determine what type of documentary evidence should be requested in technical specifications. For example, bioavailability is an important product characteristic that identifies the speed and complete-

ness with which a drug enters the bloodstream. Specific bioavailability protocols have been established for some pharmaceutical products.

Technical specifications should also specify the amount of shelf-life remaining when a medicine arrives in a country. For example:

- Products with a shelf-life of more than three years should have a minimum remaining shelf-life of 66 percent upon arrival at the port of entry.
- Products with a shelf-life of three years or less should have a remaining shelf-life of 75 percent upon arrival at the port of entry.

CERTIFICATION REQUIREMENTS

When suppliers have been prequalified, supplier certification requirements will have been already reviewed by the responsible committee. This includes prior review of the "Certificate of Pharmaceutical Product" and "Statement of Licensing Status of a Pharmaceutical Product" provided under the WHO Certification Scheme (World Health Organization, 1994, 1997b). The WHO Statement of Licensing Status of a Pharmaceutical Product appears here as Form 6.1.

For the technical specifications, however, the procurement office is advised to require that a "Batch Certificate of a Pharmaceutical Product," in accordance with the WHO Certification Scheme, accompany each product shipment. The WHO Model Batch Certificate of a Pharmaceutical Product is appended as Form 6.2.

PHARMACOPEIAL STANDARDS

Where applicable, the technical specifications should state that all products supplied be based on the *United States Pharmacopeia*, the *British Pharmacopoeia*, the *European Pharmacopoeia*, or the *International Pharmacopoeia*. The specific pharmacopeial standard for each product and year of issue must be identified. If a product is not based on a pharmacopeial standard, then a copy of the finished product specification, which is equivalent to that found in the product dossier, must be submitted for review.

LABELING REQUIREMENTS

The technical specification identifies the language of the product label, the information that should be included on the label (INN, active ingredient per unit, batch number, manufacturer's name and location), and any applicable labeling standard with which the package should comply.

PACKAGING REQUIREMENTS

Proper packaging protects a product during rough transport and extreme climatic conditions, thereby maintaining product quality. The technical specification should indicate appropriate packaging requirements, such as identification of the pharmacopeial standards with which a pharmaceutical product container must comply, requirements for suitable packaging material, tamper-resistant containers, and wall thickness of the shipping container.

Exterior packing requirements. Exterior shipping cartons should state the product name, supplier name and address, consignee name and address, and lot and batch number. All information should appear on two opposing sides of the carton to facilitate transit to its final destination.

Literature requirements. Literature that extensively describes the product, including directions for use, contraindications, and so on, should be requested from the supplier. The national MRA establishes regulations concerning medicine information requirements. Final responsibility for the text, however, rests with the manufacturer.

PRODUCT QUANTITY AND DELIVERY REQUIREMENTS

A schedule of requirements provides a concise description of a medicine, the quantity required, and any technical specifications unique to it. Medicines should be identified by their INN or generic name, the strength of each component, the basic unit and package size, and the total number of packages required (Management Sciences for Health, 1997).

Select suppliers

The supplier from which one chooses to purchase medicines is closely tied to the procurement method. Four methods for procuring medicines include direct procurement, competitive negotiation, open bid, and restricted bid—the most preferred method.[8] Open bid, restricted bid, and competitive negotiation require that several suppliers compete for the right to sell and deliver medicines. This competition among suppliers generates favorable pricing. Direct procurement, however, involves a single supplier and does not usually result in favorable pricing. This procurement method is used primarily for small-value and emergency purchases.

When several suppliers compete to provide products, a qualification process must be established to eliminate suppliers of substandard products. Supplier qualification can occur at two points in the procurement process: Before requests for bids are issued and after bids have been received.

In a prequalification process, a supplier's technical capacity, financial capability, and reputation are evaluated before the request for bid is released; thus, only prequalified suppliers receive a request for bid. In postqualification, the evaluation process is conducted after bids have been received.

Among the three competitive procurement methods (open bid, restricted bid, competitive negotiation), restricted bidding with prequalification of suppliers is the preferred method for procuring medicines. This method is discussed in more detail below.

CONDUCT LIMITED BIDDING WITH PREQUALIFIED SUPPLIERS

Prequalification focuses on the technical and financial capabilities of prospective suppliers, without reference to price or contractual conditions.[9] Standard prequalification procedures include gathering information about supplier reliability and medicine quality; inspecting samples and manufacturing facilities; and, if necessary, conducting laboratory tests of medicines with a high potential for problems.

Prequalification can occur outside of or parallel to the actual tendering process so that the strict timelines that govern the tendering process do not need to be applied. The prequalified supplier list must be updated from time to time to add more suppliers and to improve competition and lower prices.

The primary purpose of prequalification is to ensure that a supplier is properly registered and that products are manufactured under GMP conditions and are approved for marketing

in the country of origin. Key components of a comprehensive supplier prequalification system may include:

- Product registration
- Product certificates from the WHO Certification Scheme
- Supplier questionnaire
- Reference checks and information exchange between medicines regulatory authorities
- Site inspection, if appropriate
- Targeted laboratory testing, if necessary
- Informal local information
- Using suppliers that are prequalified by reputable international agencies.

Product registration. Medicine manufacturers, suppliers, or their agents are advised to submit a product dossier and certifications that are required by the relevant authority to officially register the product for distribution and use.

Product certificates from the WHO Certification Scheme. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (World Health Organization, 1994, 1997b) is an international voluntary agreement designed to enable countries with limited medicines regulatory capacity to obtain partial assurance from exporting countries about the safety, quality, and efficacy of the medicines they plan to import.

When conducting supplier prequalification, the procurement office is advised to request the certificates described below.[10]

Certificate of a pharmaceutical product (product certificate). A certificate of a pharmaceutical product is issued by an MRA in the exporting country and confirms whether a medicine is approved for use in the exporting country or, if it is not approved, explains the reasons why it is not. The document certifies whether the manufacturer's production facility is inspected regularly and meets GMP requirements, and confirms that product information included with the certificate is approved for use in the exporting country.

Statement of licensing status. A statement of licensing status confirms that a license has been issued for the product for use in the exporting country (World Health Organization, 2000b).

The WHO Certification Scheme is an inexpensive way for a procurement office to gather product quality information. However, the reliability of the certificates issued under the WHO scheme largely depends on the reliability and capability of the exporting country's medicines control authority.

Supplier questionnaire. A questionnaire can obtain data about a supplier's business, manufacturing practices, and products. A sample questionnaire to use in prequalifying suppliers of pharmaceutical products is appended to this chapter as Form 6.3. The questionnaire requests the information described below.

Business information. Business information includes the size of the business in terms of personnel, capital value, and sales turnover; the type of activity the supplier conducts (manufacturing or wholesale); whether products are manufactured only for export or whether they

are sold in the country of origin; and the names of the commercial director and the general manager, and samples of their signatures.

Manufacturing information. Manufacturing information includes the number of medicines manufactured; a copy of GMP[11] and other types of certification (e.g., International Organization for Standardization, or ISO); information about the business; manufacturing license; whether products are manufactured by the company and in which manufacturing plant or whether manufacturing is contracted to others; and information about the production site, such as capacity, air, and water treatment systems.

Quality information. Quality information includes such data as whether or not a manufacturer maintains a quality control laboratory; the number of specialized personnel working in the quality control laboratory; quality standards used for testing products; whether written procedures exist for cleaning, training, and product recalls; whether stability tests are routinely conducted for each product; and the names and specimen signatures of the key staff responsible for the quality control system.

Product information. Product information includes a list of active pharmaceutical ingredients and their source of manufacturing, drug master file registration number and country of registration, trade name, dosage form, regulatory status in the country of origin, Certificate of Pharmaceutical Product according to the WHO Certification Scheme, finished product specification, stability information, therapeutic equivalence, and storage conditions.

Reference checks and information exchange between medicines regulatory authorities. A procurement office may wish to contact MRAs in other countries and purchasing groups, such as the International Dispensary Association, to obtain information regarding product or supplier problems. Existing networks for information exchange between medicines regulatory authorities such as the WHO Electronic Discussion Group for Drug Regulatory Authority (WHO DRA) can also be contacted.

Site inspection. Under ideal circumstances, a supplier's manufacturing facility should be inspected for GMP compliance. However, for an inspection to be effective, the investigator must be trained in GMP inspection procedures. This is often not a feasible option due to a lack of qualified inspectors and funds. If serious concerns about a potential supplier's GMP and quality control procedures exist, a procurement office should consider hiring a qualified independent consultant to perform the site inspection.

Targeted laboratory testing. For all new suppliers, the procurement office arranges a visual inspection of a sample product's package and label. Procurement officers must bear in mind, however, that samples provided by the supplier may not represent the actual product that will be delivered. Some targeted products should also undergo the next level of evaluation, which is laboratory testing. These submitted samples should be retained for later comparison with delivered products.

Laboratory testing is an option under limited circumstances; for example, when concerns exist about specific products or categories of products, such as medicines with a high potential for dissolution problems. When laboratory testing is required, the procurement office arranges for the national reference laboratory to conduct the tests or contracts with a qualified, independent laboratory to perform testing.

Informal local information. Information from local agencies and individuals who have had experience with a potential supplier can be helpful in evaluating previous supplier performance. While obtaining this information is often the least time-consuming option, it must be assessed carefully because opinions may be biased.

Using suppliers prequalified by reputable international agencies. For certain medicines and pharmaceuticals, international agencies conduct their own prequalification process in accordance with internationally accepted qualification procedures. For example, the WHO prequalifies some vaccines, which allows other United Nations agencies, such as UNICEF, to procure those vaccines from the manufacturer. The Quality Assurance and Safety of Medicines unit of the WHO Essential Drugs and Medicines Policy Department conducts a prequalification scheme for manufacturers of medicines to treat HIV/AIDS, malaria, and tuberculosis.[12] Purchasers may consider using suppliers whose products have been prequalified by such international agencies. Purchasers should note, however, that such prequalifications are always product-specific, and do not constitute prequalification of a supplier's entire product line.

COMPILE PREQUALIFICATION INFORMATION

The procurement office assembles information obtained by the methods described above and submits the data it has compiled to the designated supplier prequalification committee for review. This committee should be a diverse group of health care managers and technical personnel, including quality assurance experts and pharmacists. The committee evaluates the information and selects suppliers for the prequalified list.

QUALIFY MANUFACTURERS AFTER BIDS ARE RECEIVED (POSTQUALIFICATION)

The postqualification process is similar to that of prequalification. However, there are usually more suppliers to screen because postqualification is often conducted via an open bid process. The additional suppliers that must be evaluated, along with a limited evaluation window, can place a significant burden on a procurement office with limited capacity. This is why restricted bidding, along with a prequalification process that uses a combination of methods discussed above, is often the preferred method for procuring pharmaceutical products.

Prepare bid documents

Bid documents are prepared after appropriate medicines have been selected, requirements have been quantified, technical specifications have been developed, and suppliers have been prequalified.

Bid documents describe the purchaser's requirements and procedures for the procurement process, providing the pertinent information a supplier needs to properly prepare and submit a responsive bid. Standard bid procedures usually include the following documents:

Invitation to bid. An invitation to bid describes the overall procurement process and conditions for accepting bids, and explains when bids are due.

Instructions to bidders. Instructions to bidders describe how bidders are to submit documents, criteria against which they will be evaluated, award procedures, and whether or not bid or performance bonds are required.

Technical specifications. Technical specifications identify specific products and certification requirements.

Conditions of contract. The conditions of a contract contain general and specific contract conditions, such as patent protection rights,[13] that will be included in the contract award.

Product quantity and delivery requirements. Product quantity and delivery requirements identify specific product, quantity, and delivery schedule requirements.

A bid document should also identify the quality assurance testing requirements that will be performed on finished products for acceptance of consignments and should identify the public pharmacopeial standards to be used as references. The document should also require the following information:

- A certificate of analysis, indicating the tests that were conducted against specifications and actual quantification of results that were obtained.
- Reference standards and specifications, provided by the manufacturer, for products with no known public specifications.
- Method validation, if analytical methods are not described in pharmacopeial references.

Release bid documents

Bid documents are combined to become the bid document package, sometimes referred to as a bid book. The bid book is forwarded to prequalified suppliers who are required to submit their bid within a specified time period.

Receive and evaluate bids

Bids from suppliers are submitted in sealed envelopes to the procurement office by the date stipulated in the bid documents. Bids must be stored in a secure location until the scheduled time for opening. Bids are usually opened in the presence of participating companies. Bid documents are traditionally evaluated by a committee that uses a set of pre-established criteria. The committee includes personnel with technical expertise to examine the product documentation and certification submitted by suppliers.

In restricted bidding with prequalified suppliers, the bid committee focuses on product prices, the supplier's commitment to comply with the proposed contract terms and conditions, and its capacity to deliver the products in accordance with delivery requirements.

Award contract

When the winning bids have been selected, the successful bidder is notified that it has been awarded the contract and may be required to raise a bid bond in the form of a letter of credit. The procurement office works with its contracts office to develop a contract with the chosen supplier. A contract identifies the products, international shipping terms,[14] payment terms, and methods for resolving contract disputes. The pact identifies the responsibilities of both parties, as well as contract terms and conditions, and becomes a legally binding document between the purchaser and the seller. A contract includes technical specifications about the product and quality assurance requirements previously identified in the original bid documents, as well as modifications agreed to by both parties.

Inspect products

Three inspection methods can help assess product quality:

- Inspection of documents and certifications
- Visual inspection of the product, including labeling, dosage form, strength, and packaging
- Laboratory or physical testing of the product.

Determining which level of inspection to conduct depends on the results of previous experiences with the supplier.

REVIEW DOCUMENTS

The supplier will submit technical specification documents, such as certificate of batch analysis, for each manufacturing lot in the shipment, and certification of compliance with GMP. The procurement office arranges for personnel to review the documents to confirm that the supplier performed the required tests during product manufacture and that reported test results meet GMP standards.

Chapter 9 contains additional information on the subject of document review.

PERFORM VISUAL INSPECTION

During visual inspection, medicines are randomly selected and inspected to confirm that quantity, dosage form and strength, packaging, labeling, and markings comply with the requirements stated in the contract.[15] Visual inspection will indicate signs of product and package damage, and deterioration. If defects are discovered during a visual inspection, an internationally recognized verification bureau should assess the damages and discrepancies, and write a report that can serve as the basis for an insurance claim. The decision to accept or reject a lot is based on a comparison of the inspection results to the acceptable quality level identified in the contract. A common practice should be to outline inspection and sampling procedures, indicating what measures to take when the sample fails the set standards.

Chapter 9 contains additional information on the subject of visual inspection.

CONDUCT LABORATORY OR PHYSICAL TESTING

Laboratory (physical) testing of pharmaceuticals can be time-consuming and expensive, and is usually reserved for products that meet the following criteria:

- They have the greatest potential for bioavailability or stability problems.
- They are from new or questionable suppliers.
- They have been the source of previous complaints.
- They are produced by manufacturers that have not yet received GMP certification.

The tests to be performed depend on the product and reason for testing (Management Sciences for Health, 1997). To conduct laboratory testing, the procurement office must include a clause in its contract that grants the buyer the right to test the products of its choice. The results from these tests should be compared with those of the original samples that were submitted for earlier testing.

Samples are randomly selected and forwarded to a national reference laboratory or to an independent laboratory selected by the procurement office. If laboratory tests indicate that the product does not comply with key technical specification requirements, the procurement office notifies the supplier that it rejects the lot. The purchaser should pay for laboratory testing to ensure objective results.

Monitor supplier performance and product quality

In countries that have an effective national medicines policy and a functional MRA, a national problem-reporting system will allow supply chain personnel and health care workers to report suspected or confirmed problems with specific products.

Reports of problems generated by a national reporting system, along with the results of any actions taken or tests conducted, should be forwarded to the procurement office to use when evaluating the supplier in the future.

If a medicine or product is determined to be defective, it must be recalled immediately. An effective product-recall system generates information that the procurement office uses to notify the supplier about replacing the defective product; the manufacturer or supplier is responsible for recall costs. If the supplier does not respond adequately to the request to replace the product, the procurement office can withhold payment until the defective product is replaced.

The procurement office should develop a formal monitoring system that tracks the following data:

- Lead time
- Compliance with pricing terms
- Partial shipments
- Compliance with remaining shelf-life requirements
- Compliance with packaging and labeling instructions
- Compliance with technical specifications
- Compliance with contract terms
- Summary of outcomes of performed inspections.

If performance monitoring indicates that a particular supplier is consistently having product or performance problems, then the procurement office and its technical committees should determine the appropriate course of action. Depending on contract conditions, options might include the following:

- Nullifying the contract without compensating the supplier and obtaining products from other sources
- Recovering any losses sustained as the result of the supplier's failure to perform
- Delisting the supplier from the prequalified list of suppliers
- Imposing fines, if this option is included in contract terms.

Carry out preshipment inspection

The procurement office must decide whether to conduct a preshipment inspection. Because the additional time required to exchange a defective product for a good product can have a negative impact on a health care program, preshipment inspection can prevent unacceptable products from entering the market. Several independent international companies specialize in preshipment inspections. Inspection requirements are always included in the contract issued to the supplier.

Carry out postshipment (receipt) inspection

Even when preshipment compliance inspection occurs, all shipments still should be inspected when they arrive in a country to ensure they were not damaged in transit. Receipt inspection occurs at the point the product first enters the country and should include the following:

- A review of all shipping documentation
- An inspection of all shipping cartons for damage
- An inspection of the contents of any damaged shipping carton
- Tests of a random sample of the product; guidelines for random sampling inspection can be found at the end of this chapter (Annex 6.1).

Damaged products must be documented, and the supplier should replace the products. If damage is not apparent, then additional cartons should be opened to confirm that contents comply with the shipping documents and contract requirements (World Health Organization, 2002d; Annex 1).

Additional Procurement Options

Additional options for securing medicines include hiring the services of a procurement agent, international agents, and pooled procurement.

Procurement agents

If procurement is the job of staff with limited procurement training, a government may wish to consider retaining the services of a procurement agent. Some international agencies offer procurement services for specialized products. For example, UNICEF provides procurement services for vaccines, and the United Nations Population Fund (UNFPA) provides procurement services for reproductive health medicines and supplies. Nongovernmental organizations also provide procurement services. Be sure to verify the agent's experience, expertise, and qualifications before making a selection.[16]

Direct procurement from international agencies

The Global Drug Facility of the Stop TB partnership (http://www.stoptb.org/gdf/) offers procurement services to national TB programs that lack the staff and capacity to prequalify manufacturers, oversee quality control of TB medicines, and manage procurement agents.

Regional pooled procurement

To procure large quantities of drugs and thereby increase the buying power and the advantages this entails—lower prices and better services from the seller—regional pooled procurement should be considered.

In pooled procurement, several buyers—countries or states of a federal nation—combine their drug purchases into a consolidated order and issue one tender for the total quantities they need.

Pooled procurement has proven difficult to organize and to sustain, although a few successful examples of regional pooled procurement exist, such as the Pan American Health Organization for vaccines, Organization of Eastern Caribbean States Pharmaceutical Procurement Service for pharmaceuticals, and the Gulf Cooperation Council for bulk and direct purchasing.

Regional pooled procurement works only if all participants gain. Several conditions will increase the chances of success. These include participating countries and states having the following points in common:

- Similar population size and economic strength
- Other formalized cooperative bodies already in place
- Similar public health structures
- Identical essential drug lists
- National MRAs that recognize each other or appoint an MRA to handle product registration on behalf of the others.

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6 See Chapter 5 for further discussion of the roles and responsibilities of a medicines regulatory authority.

7 See "Limited bidding with prequalified suppliers" in this chapter.

8 Although these procurement methods are common in many countries, a nation's procurement office must review national legislation to determine the public tendering requirements it must follow. Donor requirements for tendering must also be addressed. The information in this section is based on that contained in *Practical Guidelines on Pharmaceutical Procurement for Countries with Small Procurement Agencies* (World Health Organization, 2002d). The World Bank has also developed a trial prequalification document, "Standard Pre-qualification Document: Procurement of Health Sector Goods" (April 2002).

9 Information in this section is based on that contained in *Practical Guidelines on Pharmaceutical Procurement for Countries with Small Procurement Agencies* (World Health Organization, 2002d).

10 Another important document requested by the purchaser in the bid documents is the WHO "Batch Certificate of a Pharmaceutical Product." Because the document is a production record, it is not requested in a prequalification exercise, but is submitted by the manufacturer after production to confirm that individual batches conform to quality specifications.

11 Good manufacturing practices should comply with World Health Organization requirements.

12 For more information on the WHO prequalification scheme, visit: http://mednet3.who.int/prequal/tub/tubdefault.htm. For information on the Global Drug Facility, see http://www.stop tb.org/gdf/.

13 At its 2001 meeting in Doha, Qatar, the World Trade Organization's "Declaration on TRIPS and Public Health" acknowledged that patents and prices can be an obstacle to developing countries' access to medicines.

14 INCO (international cooperation, or international commercial) terms are internationally accepted commercial terms that define the roles and responsibilities of the buyer and seller in arranging transportation, and clarify when ownership of merchandise occurs. INCO terms are used in conjunction with a sales agreement or other sales transaction method; for example, FOF (Free On Board) and CIF (Cost, Insurance, and Freight). For additional information, see http://www.globalshippers.com/Global-Shipping-Tools/INCO-Terms.html.

15 For guidance on conducting random sampling, see the WHO guidelines for sampling of pharmaceuticals and related materials intended to replace the sampling procedure for industrially manufactured pharmaceuticals, to be published in the WHO Technical Report Series in early 2005. Also see http://www.aqlinspectorsrule.com/.

16 References should be obtained and contacted to confirm that the procurement agent being considered has a reputable history of service, the necessary technical expertise to procure the medicines requested, and provides services at a reasonable cost.

Checklist 6.1
Establishing an effective procurement unit

NATIONAL POSITION OF A PROCUREMENT UNIT

- ☐ A procurement unit should have a formal legal status within a national administrative structure.
- ☐ All stakeholders, including the legislature and MRA, should recognize the procurement office's structure.
- ☐ Remedies must be in place to enforce compliance.

INTERNAL ORGANIZATION OF A PROCUREMENT UNIT

- ☐ A procurement unit should have a central board and executives.
- ☐ The unit should adopt a code of conduct or practice.
- ☐ The unit should have clear employment contracts specifying positions, responsibilities, and powers.
- ☐ Standard operating procedures for all major functions and activities should be established.
- ☐ Personnel should consist of at least the following:
  - ☐ One lawyer, if not on a permanent staff basis, certainly as a part-time resource person
  - ☐ One pharmacist
  - ☐ One technical officer
- ☐ A systematic recording and monitoring system should be in place.

INDEPENDENT TENDER COMMITTEE

- ☐ Standard operating procedures, such as identification of committee members, rules governing procedures for review of tenders, and rules governing the requirement for a quorum must be established.
- ☐ Members include specialists in procurement, especially in tendering and contracting; stakeholders, such as representatives of the Ministry of Health or Ministry of Finance; and representatives of program offices that order, receive, and distribute pharmaceuticals.

QUALITY ASSURANCE

- ☐ Define appropriate standard operating procedures, including requirements for product inspection and testing, sampling methods, measures to be taken when testing falls short of standards, product monitoring, and reporting requirements.
- ☐ Assign pharmacists trained in quality principles the responsibility for quality assurance.
- ☐ Apply the WHO certification scheme, which includes a review of the Certificate of Pharmaceutical Product and Statement of Licensing Status of a Pharmaceutical Product, when prequalification occurs; and supply a Batch Certificate of a Pharmaceutical Product for each shipment.
- ☐ Develop and apply sampling procedures consistent with GMP.
- ☐ Create a quality control laboratory or arrange to contract preshipment and postshipment inspection testing services.

- ☐ Perform systematic monitoring of product quality throughout the supply chain through random product sampling and inspection according to specific procedures.
- ☐ Establish a mechanism for reporting product quality problems.
- ☐ Establish procedures for recalls and legal recourse.

PURCHASING PROCEDURES

- ☐ Determine quantities and sources on a systematic basis.
- ☐ Establish procedures for assuring financial resources.
- ☐ Establish procedures for selecting procurement methods.
- ☐ Establish prequalification procedures for products and suppliers.

PORT CLEARING AND DOCUMENTATION

- ☐ Employ specialized staff.
- ☐ Establish and adopt procedures for port clearing and documentation.
- ☐ Establish written protocols for handling cases of abnormalities.

Form 6.1
WHO Certification Scheme: Model Statement of Licensing Status of Pharmaceutical Products Issued by Exporting Country's MRA

No. of Statement

Exporting (certifying) country's MRA.

Importing (requesting) country's company or MRA.

Statement of Licensing Status of Pharmaceutical Product(s).[1]

This statement indicates only whether or not the following products are licensed to be marketed in the exporting country.

Applicant (name/address):

Name of product	Dosage form	Active ingredient(s)[2] and amount(s) per unit dose:	Product license no. and date of issue[3]

The certifying authority undertakes to provide, at the request of the applicant (or, if different, the product license holder), a separate and complete Certificate of a Pharmaceutical Product in the format recommended by WHO, for each of the products listed above.

Address of certifying authority:

Name of authorized person:

Telephone/fax numbers:

Signature:

Stamp and date:

This statement conforms to the format recommended by the World Health Organization (general instructions and explanatory notes below).

GENERAL INSTRUCTIONS

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

The forms are suitable for generation by computer. They should always be submitted on paper, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

EXPLANATORY NOTES

[1] This statement is intended for use by importing agents who are required to screen bids made in response to an international tender and should be requested by the agent as a condition of bidding. The statement indicates that the listed products are authorized to be placed on the market for use in the exporting country. A Certificate of a Pharmaceutical Product in the format recommended by WHO will be provided, at the request of the applicant and, if different, the product license holder, for each of the listed products.

[2] Whenever possible, use International Nonproprietary Names or national nonproprietary names.

[3] If no product license has been granted, enter "not required," "not requested," "under consideration," or "refused" as appropriate.

Form 6.2
WHO Certification Scheme: Model Batch Certificate of a Pharmaceutical Product

Manufacturer's Official[1] Batch Certificate of a Pharmaceutical Product

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).

1. No. of Certificate:

2. Importing (requesting) authority:

3. Name of product:

3.1. Dosage form:

3.2 Active ingredient(s)[2] and amount(s) per unit dose:

3.2.1 Is the composition of the product identical to that registered in the country of export? yes/no/not applicable[3] (key in as appropriate)

If no, please attach formula (including excipients) of both products.

4. Product license holder[4] (name and address):

4.1 Product license number[4]:

4.2 Date of issue[4]:

4.3 Product license issued by[4]:

4.4 Product certificate number[4,5]:

5.1 Batch number:

5.2 Date of manufacture:

5.3 Shelf-life (years):

5.4 Contents of container:

5.5 Nature of primary container:

5.6 Nature of secondary container/wrapping:

5.7 Specific storage conditions:

5.8 Temperature range:

6. Remarks[6]:

7. Quality analysis:

7.1 What specifications apply to this dosage form? Either specify the pharmacopoeia or append company specifications.[7]

7.1.1 In the case of a product registered in the exporting country, have these company specifications[7] been accepted by the competent authority?
yes/no (key in as appropriate)

7.2 Does the batch comply with all parts of the above specifications?
yes /no (key in as appropriate)

7.3 Append certificate of analysis[8]

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person:

Telephone No.: Fax No.:

Signature of authorized person:

Stamp and date:

General instructions

Please refer to the guidelines for full instructions for completing this form and information on the implementation of the Scheme.

These forms are suitable for generation by computer. They should always be submitted on paper, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

Certification of individual batches of a pharmaceutical product is undertaken only exceptionally by the competent authority of the exporting country. Even then, it is rarely applied other than to vaccines, sera, and biological products. For other products, the responsibility for any requirement to provide batch certificates rests with the product license holder in the exporting country. The responsibility to forward certificates to the competent authority in the importing country is most often assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the competent authority in the exporting country. A copy should be sent to the product license holder.

1. Strike out whichever does not apply.

2. Use, whenever possible, International Nonproprietary Names or national nonproprietary names.

3. Not applicable means that the product is not registered in the country of export.

4. All items refer to the product license or the Certificate of a Pharmaceutical Product issued in the exporting country.

5. This refers to the Certificate of a Pharmaceutical Product as recommended by the World Health Organization.

6. Indicate any special storage conditions recommended for the product as supplied.

7. For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.

8. Identify and explain any discrepancies from specifications. Government batch release certificates issued by certain governmental authorities for specific biological products provide additional confirmation that a given batch has been released, without necessarily giving the results of testing. The latter are contained in the manufacturer's certificate of analysis.

This model certificate is available on the WHO/EDM website at: http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifscheme.shtml.

Form 6.3 Sample questionnaire for prequalification of suppliers for pharmaceutical procurement

Country:

This questionnaire is intended to facilitate the process of prequalifying pharmaceutical suppliers. Information derived from forms submitted by potential suppliers serve as the basis for evaluating companies and assessing their manufacturing and production capabilities in line with good manufacturing practice and quality standards. This form contains four parts:

Part I	Business Information
Part II	Manufacturing Information
Part III	Quality Information

Applicants for prequalification should complete one form for Parts I and II. Part III requires that a separate form be completed for each product being offered for prequalification.

Information provided by potential suppliers seeking prequalification must be regarded as confidential information.

I. BUSINESS INFORMATION

1. Name of company:

Year established:

Form of company:

- ☐ Individual
- ☐ Partnership
- ☐ Corporation
- ☐ Other (specify)

Legal status:

Trade register number:

VAT number:

License number (attach copy):

2. Address:

Country:

Telephone: Telefax:

Telex: E-mail:

Please attach a company organizational chart.

3. Type of activity carried out by the company

☐ Manufacturer	☐ Wholesaler
☐ Branded products	☐ Branded products
☐ Generic products	☐ Generic products
☐ Medical supplies	☐ Medical supplies
☐ Laboratory reagents	☐ Laboratory reagents
☐ Other products *(specify below)*	☐ Other products *(specify below)*

Indicate% of annual turnover:

Pharmaceutical formulations:	%
Bulk drugs:	%
Medical Supplies:	%

☐ Products manufactured for export
☐ Sold only to the local market
☐ Both

4. Names and addresses of international pharmaceutical companies, parent companies, and/or subsidiaries and associated companies with whom there is collaboration or joint venture, if any:

Company	Address

5. Employees:

Total:

Management:

R&D:

Sales:

Administrative:

Others (specify):

6. Capital value of the company (specify currency)

(a) Authorized capital:

(b) Paid-up capital:

(c) Administration:

7. Annual sales turnover in the previous three years. Split export and domestic sales (specify currency).

Annual turnover	Domestic sales
Exports	Year

II. MANUFACTURING INFORMATION.

1. Total number of drugs manufactured: (provide list of manufactured products)

2. Are all manufacturing operations (processing, packaging, labeling) carried out internally?
☐ Yes ☐ No

If No, attach a list of pharmaceuticals and raw materials manufactured by other companies and marketed by your company. Please give the names of the companies for each item.

Product	Manufacturer	Address
(1)		
(2)		
(3)		

3. Provide details whether pharmaceutical products and raw materials manufactured by your company are exported to other countries.

Pharmaceutical product/ raw material	Country	Generic Name	Trade Name
(1)			
(2)			
(3)			

4. State reasons why products manufactured by your company are not marketed in the country of origin.

Generic Name	Trade Name	Reason
(1)		
(2)		
(3)		

5. Does your company have GMP certification?

☐ Yes (attach a copy of the GMP certificate if any)
Certified by:

☐ No

Indicate whether your company has other types of certification

☐ Type of ISO certification:

☐ WHO Certification Scheme

☐ Others (specify)

Attach Certificates of Good Manufacturing Practices (GMP, ISO, or Certificates of Pharmaceutical Products according to WHO Certification Scheme) covering each item you propose to export.

6. Does your government carry out inspections and controls on the production of drugs in your country?

☐ Yes ☐ No
If Yes, give date of last inspection:

7. Has your company been inspected by other governments, organizations or clients?

☐ Yes ☐ No
Inspected by: Year Outcome

8. Have products manufactured by your company been exported to other countries?

☐ Yes ☐ No

If Yes, supply details:

☐ Country or (countries):

☐ By public procurement organization:

☐ By private importer(s):

9. Date, number, and expiry date of current business license or permit

Date:

Number:

Expiry Date:

10. Date, number, and expiry date of manufacturing license or permit.

Date:

Number:

Expiry Date:

11. If you are a wholesaler, obtain the following information from the manufacturers of product you wish to offer.

A. Provide full details about the manufacturer (company name and address), with product lists and brochures of the manufacturing plants, laboratories, etc.

Manufacturer:

Address:

B. Are the products in the product list produced routinely by the company?
☐ Yes ☐ No

C. Or only occasionally on request?
☐ Yes ☐ No

D. Number of specialized personnel involved in the manufacture of pharmaceuticals (exclude administrative personnel)

Pharmacists:

Chemists:

Others:

12. Origin of manufacture

A. Are the products manufactured by your company manufactured under contract by other companies or repackaged?
☐ Manufactured
☐ Repackaged
☐ Manufactured under contract

B. If any products are manufactured under contract, attach a list of such products with the name and address of the manufacturer for each product.

Product	Manufacturer	Address
(1)		
(2)		
(3)		

C. If any products are repackaged, attach a list of such products with the name and address of the manufacturer for each product.

Product	Manufacturer	Address
(1)		
(2)		
(3)		

13. Do other companies package any of the products you manufacture?

☐ Yes ☐ No

If any products are repackaged, attach a list of such products with the name and address of the manufacturer for each product.

Product	Manufacturer	Address
(1)		
(2)		
(3)		

Provide detailed information on the quality assurance procedures followed.

14. Do you manufacture sterile products?

☐ Yes ☐ No

15. Do you manufacture beta-lactam antibiotics?

☐ Yes ☐ No

If Yes, are these production facilities in a separate building?

☐ Yes ☐ No

16. Production site. Are the production premises located in the same place as the main office?

☐ Yes ☐ No

If not, indicate address of the production premises:

Address:

If there is more than one production site, describe the production site as follows:

	Production site	Address
No. of products		
Production capacity		
Air-treatment system		
Quality of in-process water		

List the products from the different production sites:

Production site		Products	
(1)	(4)	(7)	(10)
(2)	(5)	(8)	(11)
(3)	(6)	(9)	(12)

II. QUALITY INFORMATION

1. Do you maintain your own quality control laboratory?

☐ Yes ☐ No

2. Do you hold any quality certifications or accreditations?

☐ Yes ☐ No

3. Number of specialized personnel working in your quality control laboratory (excluding administrative personnel).

Pharmacists:

Chemists:

Others:

4. List names and addresses of quality control laboratories used in addition to or in lieu of your own laboratory.

5. Are all raw materials completely tested prior to use or is a Certificate of Analysis accepted?

☐ Yes ☐ No ☐ Certificate of Analysis

6. Quality standards

☐ BP Edition ☐ USP Edition ☐ EP Edition ☐ IP Edition
☐ JP Edition ☐ CP Edition ☐ Other:

Are all recommended tests carried out?

☐ Yes ☐ No

If No, state reason why not:

Are additional tests carried out?

☐ Yes ☐ No

If No, state reason why not:

7. Are control samples of each batch retained?

☐ Yes ☐ No

8. Do you have written cleaning procedures?

☐ Yes ☐ No

9. Do you record the training of your employees according to a training program?

☐ Yes ☐ No

10. Do you have a written recall procedure?

☐ Yes ☐ No

11. Do you have a written procedure on how to address complaints?

☐ Yes ☐ No

12. Name and title of the authorized person(s) responsible for batch release:

Name:

Title:

Experience in pharmaceuticals: years

13. Name and qualification of the head of the Quality Control department:

Name:

Qualification:

Experience in pharmaceuticals: years

14. Indicate whether you perform quality tests conducted routinely:

- ☐ Active starting materials
- ☐ Nonactive starting materials
- ☐ Packaging materials
- ☐ Intermediate products
- ☐ Bulk products
- ☐ Finished products

15. Are all quality control tests performed internally?

☐ Yes ☐ No

If No, list tests performed by external laboratories:

Tests	Laboratories	Address

16. Explain process of approving sources for starting materials and describe basis for approving specifications of starting materials.

17. Do you conduct tests on each container of the active starting material?

☐ Yes ☐ No

If not, explain your way of sampling:

18. Do you test each container of non-active starting materials?

☐ Yes ☐ No

If not, describe method of sampling:

19. Are you willing to reveal the sources of starting material? (Information will be deemed confidential.)

☐ Yes ☐ No

20. Are stability tests routinely conducted for every product?

☐ Yes ☐ No

If No, state reason why not:

21. For each batch, check the procedures that are routinely performed:

☐ Batch numbers and control numbers of each component
☐ Weighed quantities double-checked and signed off for each component
☐ Acceptance record of each component
☐ Date and time of each stage of production
☐ Identification of equipment used
☐ Name of persons in charge at each stage
☐ In-process control results
☐ Environment control results
☐ Remarks on production incidents
☐ Comments on not following the master formula
☐ Yield and reconciliation
☐ Packaging material batch numbers
☐ Line clearance signoff
☐ Result of quality control of end product
☐ Inspection checks and test results, dates and signatures of inspecting officials

22. Explain procedure for releasing batches of finished products:

23. Do you keep samples of each batch?

☐ Yes ☐ No

Indicate how long do you keep the samples: years

24. Are these kept in the original containers?

☐ Yes ☐ No

25. Attach a detailed account of the current quality assurance system in your company. A quality assurance manual or handbook may be submitted.

26. Do you carry out inspections or quality audits of your own suppliers?

☐ Yes ☐ No

If Yes, describe audits in detail:

27. Describe your storage facilities:

III. PRODUCT INFORMATION (PLEASE FILL OUT ONE FORM FOR EACH PRODUCT)

1. Active Pharmaceutical Ingredient(s)

Indicate whether product has any of the following:

☐ Certificate of Suitability to the European Pharmacopoeia (CEP)

Certificate No.:

☐ The CEP is in our possession (including annex, if any).

☐ Drug Master File (DMF)

Registered in (country):

Registration no.:

☐ The full or open part of the DMF is in our possession.

☐ The full or open part of the DMF is in possession of the manufacturer.

Manufacturer:

Country:

2. Trade Name of the Product:

Dosage form: ☐ Tablets ☐ Capsules ☐ Ampoules
☐ Vial ☐ Others (specify)

Strength per dosage unit:

Route of administration:
☐ Oral ☐ I.M ☐ I.V ☐ S.C. ☐ Other (specify)

Number of units/volume or weight per container:

Type of container:

3. Regulatory Status in Country of Origin

☐ Product registered in country of origin and routinely manufactured and marketed

License no: Year issued:

☐ Product registered in the country of origin but not currently marketed

License no: Year issued:

☐ Product registered for export only

License no: Year issued:

☐ Product not registered

4. Regulatory status in other countries.

List other countries where the product is registered and currently marketed:

Product	**Country**	**Trade Name**

5. Certificate of Pharmaceutical Product according to WHO Certification Scheme (WHO Technical Report Series No. 863 http://www.who.int/medicines/team/qsm/certifscheme.html)

☐ The Certificate of Pharmaceutical Product (based on the last format recommended by WHO)
☐ The Certificate of Pharmaceutical Product cannot be obtained from the National Drug Regulatory Authorities because:

6. Dosage Forms Formulation Dose

Oral single-drug products

Oral fixed-dose combination products

Injectable single-drug products

Injectable fixed-dose combinations

7. Production Manager

Name:

Title:

Experience in pharmaceuticals: years

8. Validation. Are all your production processes validated?

☐ Yes ☐ No

9. Do you use an approved manufacturing formula and processing instructions?

☐ Yes ☐ No

10. Finished product specification

☐ CP Edition ☐ BP ☐ USP Edition
☐ CP ☐ JP

Attach a copy of the finished product specifications

Are you willing to provide necessary information (analytical methods) for the tests to be replicated by another control laboratory?

☐ Yes ☐ No

11. Limits in % for the assay in active ingredient(s):

☐ 95–105% ☐ 90–110% ☐ Other:

Additional specifications to those in the pharmacopoeia:

Attach a copy of the model certificate of analysis for batch release.

12. Stability

Stability testing data available: ☐ Yes ☐ No

Type and conditions of satisfactory testing (without significant change):

☐ Accelerated testing

☐ 40°/75% relative humidity/6 months

☐ Other:

☐ In the same packaging as marketed

☐ In another packaging

☐ Real-time testing:

Temperature: ☐ Ambient ☐ 25°C ☐ 30°C ☐ Other:

Relative humidity: ☐ 45% ☐ 60% ☐ 70%

☐ Not controlled ☐ Other:

Period of time: ☐ 1 year ☐ 2 years ☐ 3 years ☐ other:

☐ In the same packaging as marketed

☐ In another packaging:

13. Label and insert information

Shelf-life: ☐ 2 years ☐ 3 years ☐ 4 years ☐ 5 years
☐ other:

Storage conditions (e.g., Store below 30°C, Protect from light):

Package insert: ☐ Yes ☐ No

Attach a copy of the label and package insert.

14. Therapeutic equivalence

☐ Bioequivalence study

Reference:

Reference sourced from:

Number of volunteers:

Year:

Institution, country where study occurred:

Attach a copy of the report on the bioequivalence study.

☐ Clinical study

Study design: _____

Sample size: _____

Study objective: _____

Results: _____

Year: _____

Institution, country where study occurred: _____

_____

Attach a copy of the report on the clinical study.

15. Dissolution tests _____

☐ Method: _____

_____

_____

_____

☐ Results: _____

_____

_____

_____

16. Normal batch size: _____

_____

_____

Certification

I, the undersigned (full name of the person responsible)

Name _____

Designation _____

Hereby declare that all the information given above is true, and I take full responsibility for all consequences that might arise from false or erroneous information. If required, I will co-operate with any official of the Ministry of Health in (country name) in performing personal inspection of manufacturing facilities and records.

Certification by the Ministry of Health or the official authority in charge of the control and inspection of pharmaceutical manufacturing facilities:

We hereby certify that the information given is true and that the company concerned fulfills the requirements of local regulations concerning the manufacturing of pharmaceuticals.

Name _____

Designation _____

Signature _____

Date _____

Annex 6.1
Sampling for post-delivery inspection and analysis of finished-dosage forms of medicines

General Considerations

Immediately upon receiving the goods, either in the Central Medical Stores or at the port of entry (sea, land, or air), sampling should be performed. The appropriate sampling method and procedure takes into account the following parameters, which determine the number of the samples to be taken for testing:

- Types of the products;
- Size of the consignment and its homogeneity and uniformity; and
- How the material or product is packed. (A unit to be sampled may be regarded as the transport container, e.g., 20 packs shrink-wrapped or boxed together, rather than an individual container. The required number of unit dosage forms is then withdrawn from any individual container in the selected transit container.)

Generally, the size (number of units) of individual samples will be determined by the requirements of the analytical procedure by which the product will be tested.

Ideally each sample should be examined to ensure that it is intact and checked for possible damage to the container. The contents should be inspected for uniformity and tested for identity.

In general, three independent samples (two for testing and one for retention) must be taken from different randomly selected sampling boxes, cartons, bottles, or vials. When a consignment is composed of two or three batches from the same manufacturer, a single sample taken from each batch may suffice, provided that previous experience with the product and the manufacturer has been favorable, and that there is evidence from the expiry date, or other information, that the batches were produced at approximately the same time.

Sampling Special Precautions

- There should be a standard operating procedure describing the sampling process that includes health and safety aspects of sampling.
- Given that the sampling technique itself can introduce bias, it is important that personnel carrying out the sampling should be suitably trained in the techniques and procedures used. Sampling records should clearly indicate the date of sampling, exact location, the sampled container, and the person who sampled the batch.

Sample Collector and Note for the Record

Samples are best taken by, but not limited to, an official of the MRA in the presence of an official of the central medical store, if applicable, and the consignee (e.g., the national disease program).

A 'Note for the Record' should be made up immediately and signed by the officials and relevant representatives present during samples collection.

The note for the record should contain, at a minimum:

- Date, time, and exact location where samples were taken
- Batch or lot number, product name, Air Way Bill number, and packing list number

- Number of units (tablets, capsules, etc.) taken
- Observations (see first steps in three-level testing approach, Chapter 8).

Whenever possible and appropriate, digital photographs showing deficient product, e.g., faulty packing or discolored tablets, could be attached.

Number of Samples To Be Taken

From every batch/lot, three samples each should be taken of, at a minimum, 50 dosage units (tablets, capsules, or suppositories, etc.) for single pharmaceutical active ingredient (API) solid dosage forms; and 100 dosage units per sample for fixed-dosed combinations (FDCs), i.e., preparations that have more than one API; and 10 vials per sample for single API injectables, 20 for FDCs.

Packaging and labeling of samples

The container used to store a sample should not interact with the sampled material nor should it allow contamination. The samples should be in their original "unit" packaging and labeling, if applicable. It should also protect the sample from light, air, and moisture, as required by the storage directions for the material sampled. As a general rule, the container should be sealed and tamper-resistant. Drug samples should be kept in their original packaging, especially for blisterpack preparations.

The container must be properly labeled and contain the key information as described under the section "Sample Collector and Note for the Record."

Transportation of samples to the testing laboratory

Adequate care and measures must be taken to ensure that samples, already packed and properly labeled, are transported to where the tests are performed without any physical damage to the samples that might affect the physical/visual examinations and other integrity of the products.

- Send one sample for analysis to the testing laboratory with necessary papers.
- Keep two samples at the MRA or Procurement agency and store them under controlled and prescribed conditions for future analysis in case of Out of Specifications (OoS) outcome of laboratory analysis or future problems occur with the products.
- Inform the manufacturer/supplier immediately that samples have been taken, indicating batch numbers sent for laboratory analysis; and copy the manufacturer on the test results regardless of their outcome.
- Include in the purchase contract procedures on how to handle cases of OoS outcome, e.g., recall, replacement of defective goods, destruction of defective goods, financial indemnification, etc.

Storage of samples

Collected samples must be properly packed, transported, and stored in such a way to prevent any deterioration, contamination, or adulteration. Collected samples should be stored in accordance with storage instructions for the respective drug. Closures and labels should be tam-

per-evident, that is, of a type that unauthorized opening can be detected. When opening a sample container, the analyst or the person who opens it must date and initial it.

Examples of steps for sampling

Depending on the consignment, the samples may come in pallets, cartons, or boxes.

1. Determine the number of pallets or cartons or boxes per batch in the consignment.
2. Work out, using the Table below, the number of pallets, cartons, or boxes to be checked visually and from where samples will be taken.
   - **2.1** Check physical conditions of cartons or boxes in each pallet and packaging for damages.
   - **2.2** Check that the overall labeling of the pallets, cartons, or boxes matches the packing list.
   - **2.3** Count, categorize, and record the number of defects.
3. From the total number of pallets, cartons, or boxes, randomly select, using the Table below, the number of unit packs to be examined.
   - **3.1** Check the condition of the containers for integrity of packaging material.
   - **3.2** Check the overall labeling of containers for damage.
   - **3.3** Check the labels for spelling mistakes.
   - **3.4** Check the labels for manufacturing and expiry dates.
   - **3.5** Check the contents (tablets, capsules, etc.) for shape and color consistency.
   - **3.6** Count, categorize, and record the number of defects.
4. From the number of containers selected, determine the number of samples (n value in the table below) to be taken for physical and chemical testing and for retention.

How to work out how many samples should be taken

Number of samples to be taken	Number of units (boxes or containers) in the consignment	
(n)	When a consignment is considered uniform and from a well-known supplier	When a consignment is considered non-uniform and/or received from an unfamiliar supplier
2	Up to 4	Up to 2
3	5–9	3–4
4	10–16	5–7
5	17–25	8–11
6	26–36	12–16
7	37–49	17–22
8	50–64	23–28
9	65–81	29–36
10	82–100	37 - 44

For further information resources on statistical methods for sampling refer to: ISO Standards Handbook: Statistical methods for quality control. Volume 1: Statistical methods in general. 2000, Ed. 5, 710 p., ISBN 92-67-10320-2

CHAPTER 7

Quality Assurance and Donations of Medicines

Too often, medicine donations have been a source of controversy caused by misunderstandings, misguided intentions, ignorance, or hidden motives. Medicine donations may be a part of regular development aid by governments or nongovernmental organizations to low-income countries, they may be given as a rapid response to natural disasters, or they may be provided as humanitarian aid to refugees and victims of war. Sometimes, pharmaceutical companies make large donations to specialized national programs or offer small, private initiatives to specific health facilities. Yet in many cases, the donations have been inadequate, causing more problems for the recipients rather than solving existing problems.

Giving and receiving donations should always result in a win-win outcome, whereby neither party gains at the detriment of the other. Donations should never be accepted indiscriminately, not even in emergencies, because they can endanger public health, especially when donated medicines are of poor quality or near their expiry date. Countries can and should refuse unwanted donations.

A checklist on effective donations of medicine appears at the end of the chapter (Checklist 7.1).

WHO Guidelines for Donations of Medicines

In 1996, the World Health Organization and several donor organizations developed guidelines for donations of medicines (http://www.who.int/medicines/library/par/who-edm-par-1999-4/). The guidelines were designed to improve—not discourage—the quality of medicine donations, and describe good donation practices. The guidelines may be used as a basis for a medicine donations policy.

The core principles underlying the WHO Guidelines for Drug Donations are that a donation should:

- Offer maximum benefit to the recipient
- Respect the wishes and authority of the recipient

- Not allow double-standards of quality
- Result from effective communication between the donor and the recipient.

In 1999, the guidelines were revised to allow the existing requirement—donated medicines should have a remaining shelf-life of at least one year—to be waived under special circumstances, and on the condition that the recipient institution give consent before the donation is shipped.

Ensuring Donation Quality

Donation recipients can do much to ensure they receive only quality medicines. Donors and recipients alike should formulate their own guidelines for receiving donations, based on the Guidelines for Drug Donations (World Health Organization, 1999c). National guidelines should then be incorporated into national medicines policy regulations. When possible, national guidelines should be developed in consultation with the main contractual donor partners. Once adopted, the guidelines should be disseminated to all parties involved in donating medicines to a country.

National Guidelines for Donations of Medicines

Section IV of the WHO Guidelines for Drug Donations discusses medicine donation management and offers a list of important issues to address in national guidelines. The following paragraphs are a brief explanation of those issues.

Define and prioritize medicine needs. Medicine needs should be specified according to the needs of a country's national health policy rather than based on quantities and medicine formulations proposed by donors.

Appoint a medicines donation coordinator. Appoint one officer, preferably a staff member of the MRA, who has explicit and final responsibility for all donation matters.

Describe and develop the official documentation required for medicine donations. Develop text for national guidelines for medicine donations and ensure the guidelines are adopted by the competent authorities and disseminated among all concerned departments, including the Ministry of Finance, customs, port and airport authorities, government clearing agents, etc.

Describe the criteria for accepting and rejecting donations. If the quantity of donated drugs represents only a portion of the total required, the remainder will have to be procured through commercial channels, which could affect the price one pays for the medicine.

Describe the registration requirements. Describe whether donated medicines should be registered with the MRA, exempt from registration, or follow a fast-track registration process.

Describe procedures for unacceptable products. Describe what procedures to follow when donations do not meet the national guidelines. These procedures should be defined in unambiguous standard operating procedures and should follow the MRA standard operation procedures for unacceptable substandard drugs arriving in the country.

In principle, and to the maximum extent possible, donated medicines should conform to precisely the same rules and regulations that apply to all medicines entering a country, and there should be no difference whether medicines have been received as donations, purchased on the local market, or procured internationally.

Special thought should be given to the fact that donated medicines also represent a financial value. The value of a donation should always be represented realistically and correctly. In the case of regular donor aid, the value of a donation might be deducted from the total convened amount of aid, or interest might have to be paid in cases where aid is given as a loan.

If a donation is requested and accepted, but the quantity donated represents only a part of the total requirement for that product, the remainder will have to be procured through commercial channels. In such cases, because the total requirement will be less, the buyer's negotiating power in the procurement process will also be less. In other words, the price of the drug might be higher, on a unit basis. Donations may also complicate pricing issues, particularly for revolving drug funds.

Special care should be taken to ensure that, when accepting donations, the interests of the national pharmaceutical industry are not jeopardized. A national industry that can produce good-quality products at competitive prices is an asset and ensures competition in the international medicines industry.

Medicine registration policies, import levies and duties, protection of patent rights, and the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement may all have to be considered when writing national guidelines for donations to ensure that acceptance of a donation does not violate any national or international regulations.

Emergencies

Special provisions should be made in national guidelines to receive and manage medicine donations during emergencies and disasters. These provisions could be exceptions to common national guidelines and procedures.

However, the standard medicine quality requirements must not be relaxed simply because an emergency exists, nor should medicines with a short remaining shelf-life automatically be accepted in emergencies based on the assumption that the products will be used quickly. For instance, the emergency might have disrupted the transportation and communication systems, and their delivery might actually take more time than under normal circumstances.

Many countries have a provision that normal MRA registration procedures for pharmaceutical products can be waived for donated medicines. This practice makes it possible for such medicines entering the country not to be subjected to the national guidelines for medicine donations. However, a fast-track registration process could be useful whereby the full registration can take place after medicines have been received.

Two Global Organizations

Two global institutions have been created to accelerate the fight against AIDS, tuberculosis, and malaria: The Global TB Drug Facility (GDF, http://www.stoptb.org/GDF/) and the Global

Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund, http://www.theglobalfund.org).

GDF's main activity is to make available high-quality anti-tuberculosis medicines to national TB programs and nongovernmental organizations that adhere to the internationally recognized Directly Observed Treatment Therapy Short-Course (DOTS) strategy, either in the form of grants or for direct purchase at very competitive prices.

The Global Fund finances national projects to combat the three major diseases for which it was founded. The projects it funds may include the procurement of medicines, but the Global Fund does not donate medicines nor does it prescribe how and where these medicines should be purchased.

Medicines to treat tuberculosis donated by the GDF and those procured with Global Fund monies should likewise be subject to the same national guidelines for medicine donations as medicines from other sources. There is no reason why these donations should be exempt.

Requesting an emergency medicine donation could trigger the preparation and adoption of a national medicines donation policy with close cooperation by the MRA and other national stakeholders. Assistance in preparing requests could be sought from organizations such as Management Sciences for Health (http://www.msh.org), Population Services International (http://www.psi.org), or John Snow, Inc. (http://www.jsi.org). General information on medicines donations can also be obtained from The Partnership for Quality Medical Donations (PQMD, http://www.pqmd.org).

Checklist 7.1
Effective medicine donations

- ☐ Develop the text for national guidelines to accept medicine donations.
- ☐ Ensure national guidelines are adopted by all authorities concerned *before* donations are requested or needed.
- ☐ Ensure that national guidelines for medicine donations are in line with all national provisions regarding medicine regulations, especially those governing medicine registration.
- ☐ Specify procedures for handling medicine donations based on the national guidelines in standard operating procedures and disseminate them to all staff concerned.
- ☐ Appoint one officer to coordinate and be responsible for all matters relating to medicine donations.

CHAPTER 8

Laboratory Testing and a Three-Level Approach to Testing

Pharmaceutical quality is a global concern. The lack of reliable medicine quality assurance systems in many developing countries contributes to the proliferation of diseases, particularly those that have become resistant to traditional first-line medicines. Recent reports indicate that the availability of substandard and counterfeit drugs has reached disturbing proportions in many low-income countries. Some countries are addressing this problem by developing a medicines policy that has a country-specific quality control system. A medicine quality control laboratory (MQCL) should assure the quality of all medicines used in a nation's health programs, including those manufactured locally, imported, or donated.

One way to assure the quality of a medicine is to test it, but many countries do not have an MQCL as part of their quality control system because of the high costs required to build, equip, staff, and sustain such a facility. Thus, the widespread concentration of counterfeit and substandard medicines has been exacerbated by the absence of functional MQCLs in much of the developing world.

Ideally, a nation's medicines regulatory authority (MRA) conducts product preapproval and postmarketing surveillance for locally produced and imported drugs. In reality, few countries do both, and priority should be given to postmarketing surveillance. Procurement agents also have responsibility to test products prior to distribution.

This chapter discusses critical tests for medicines, the importance of those tests, and when they should be performed for quality surveillance. A three-level testing program, and when and where these levels should be applied, are also addressed.

Medicine Quality Control Laboratory

The World Health Organization (WHO) has encouraged its member states to maintain an MQCL or to use WHO collaborating laboratories, if a member does not have its own MQCL (World

Health Organization, 2002a). WHO has also published detailed guidelines for good laboratory practices, equipment, management, and staffing of MQCLs (World Health Organization, 2002b).

Governments establish and maintain, usually through an MRA, an MQCL to conduct the required tests and assays to ensure that active pharmaceutical ingredients (APIs) and finished pharmaceutical products meet quality specifications. The capacity of an MRA to undertake quality surveillance is directly related to the operational capability of its associated MQCL.

To ensure patient safety, the role of a control laboratory must be defined in a nation's general drug legislation in such a way that the final test results can be used in law enforcement and legal action. When no independent analytical service is available to the regulatory authority, judgments about medicine quality must be based on data supplied by manufacturers or importers.

Laboratory tests

MQCLs test medicines according to specific monographs in officially accepted pharmacopeias. A monograph determines specifications of tests, references for analytical procedures, and test acceptance criteria for a specific medicine product. In general, a monograph for a solid dosage form includes acceptance range limits, identity test for APIs, dissolution test, uniformity of dosage units, assay for the content of APIs, purity, and packaging, labeling, and storage requirements. Tests are generally not performed for excipients in drug dosage forms.

If no monograph exists for a particular medicine, an MQCL usually relies on the manufacturer's specifications and data. These specifications are based on common quality criteria presented in a pharmacopeia. If a pharmacopeia is not specified in legislation, common law rests with the manufacturer's label statement and release test methods—the medicine must be what the manufacturer claims it to be as determined by the manufacturer's release methods unless those methods can be demonstrated to be inadequate.

An MQCL, depending on its capacity, can perform several tests: Identity, assay, dissolution, bioavailability, bioequivalence, impurity, and sterility. These are discussed below.

IDENTITY TEST

A pharmaceutical identity test should be considered one of the most important tests for checking the quality of a pharmaceutical product. More than 60 percent of counterfeit medicines in the world market could be detected by identity tests alone (World Health Organization, 1991). Pharmacopeial identification tests aid in verifying the identity of articles, bulk starting materials, dosage forms, and excipients. Reports indicate that counterfeit medicines often do not contain any API, or they contain the wrong active ingredient (World Health Organization, 1999a).

API identity can be determined by one or a combination of tests, such as infrared absorption, ultraviolet-visible (UV-vis) absorption, colorimetric methods, thin-layer chromatography (TLC), or high-performance liquid chromatography (HPLC).

ASSAY TEST

All treatment regimens are based on the amount of a drug per unit of time, age, or body weight. Taking more than the recommended dose of a medicine could harm patients; lower dosages may exacerbate drug resistance. Thus, the content of APIs must be determined by an

assay test. An assay test is considered to be the second-most important test for quality control because it determines a medicine's content.

DISSOLUTION TEST

Dissolution is the process by which a solid substance enters into a solvent to yield a solution. Dissolution can serve as a quality control test by providing evidence of the product's physical consistency and manufacturing process. It forms a critical regulatory and compendia requirement in the testing of solid dosage forms and quantitatively determines the *in vitro* biological availability. Thus, if *in vitro–in vivo* correlation exists, the *in vitro* dissolution test will provide assurance that a product will dissolve in the body and, through absorption, deliver its intended effects.

Several dissolution apparatuses can be used, based on the formulation and dosage form. The most commonly used apparatuses are basket-and-paddle, UV-vis spectrophotometry, and HPLC—all techniques used to analyze the dissolved APIs in the dissolution medium.

BIOAVAILABILITY/BIOEQUIVALENCE TESTS

While a dissolution test is performed *in vitro*, the real efficacy of a product in a patient is not indicated. The quality of a pharmaceutical and its behavior in the human body is achieved via bioavailability/bioequivalence (BA/BE) studies. These tests, also known as product quality testing, determine whether product batches comply with the characteristics of the batch or batches that were originally used to establish efficacy in clinical trials. For more information on BA/BE issues, see Chapter 13.

A BE test determines pharmaceutical and therapeutic equivalence between the multisource or generic product and the comparator product, using either an *in vivo* or *in vitro* approach. In most instances, BE tests are conducted *in vivo*; BE is a comparison between any two products (i.e., generic-generic, generic-innovator or, in some instances, before–after testing required by a change in a manufacturing site).

Bioequivalence indicates that a drug in two or more dosage forms reaches the general circulation at a similar relative extent. Bioequivalence evaluation compares the *in vivo* rate and the extent of drug absorption. In a standard *in vivo* BE study design, study participants receive test and reference products on separate occasions, in either single or multiple doses, with random assignment to the two possible sequences of product administration. Blood or urine samples are analyzed for the drug or its metabolite concentrations, and pharmacokinetic parameters—the peak drug concentration (Cmax), the time to peak concentration (Tmax), and the area under the curve (AUC)—are obtained from the resulting plasma/blood drug concentration. These pharmacokinetic parameters are then analyzed to determine whether the test and reference product yield comparable values.

Generic medicines are widely used in most developing countries and BE data are becoming more commonly required for registering such medicines. In most cases, national laboratories for medicines quality control do not perform BA/BE studies. These studies are usually performed by the manufacturers. However, national authorities must be able to evaluate BA/BE studies and data in a medicine's dossier during registration, and higher-capacity MQCLs might participate in these reviews. This capacity is often available through pharmacy school faculty.

Bioavailability tests indicate the measurement of the true rate and extent to which the API or active moiety is absorbed and reaches the general circulatory system from an administered

pharmaceutical dosage form. When the rate and extent of absorption is compared with the reference product, it is called relative bioavailability. When they are compared for the same ingredient via intravenous injection, it is called absolute bioavailability.

IMPURITY TEST

Impurities are foreign contaminants present in a finished dosage form. Tests to identify and quantify impurities cannot be routinely performed by most MQCLs in low-income countries due to the prohibitive cost and high technology requirements of doing so.

STERILITY TEST

Sterility is a critical property of all parenteral drug products and is required to ensure patient safety. If the monograph requires a sterility test, then no bacteria should be detected in the pharmaceutical product. A variety of methods are available to test medicine sterility; some require microbiological techniques, including a dedicated facility and equipment. Sterility tests should be performed under sterile conditions by well-trained analysts only.

Cost of laboratory testing

Laboratory testing can be very costly because of the high prices of reagents, equipment, and reference substances. Pooling samples among recipients is always recommended to decrease costs, specifically when orders are more frequent and the size of the order is small. Some countries have established cost-recovery schemes in which testing fees are charged to applicants or registrants during product registration; however, postmarketing/preshipment-related laboratory testing is usually paid for by the government. Testing fees could be charged during registration, but the test could be performed on samples obtained postapproval, postmarketing. Test results should be compared with the test results and samples that were submitted by the manufacturer.

Monitoring the Quality of Medicines

Monitoring the quality of all essential medicines, once they have been on the market in a particular country, should be a high priority for medicines regulatory authorities. Testing is the only way to check quality. The same standards should be applied to all medicines, whether they are manufactured locally, imported, or received as a donation. Each MRA and procurement agency should have access to a quality control service.

Sampling medicines for testing

Countries that do not perform quality testing for all batch or lot numbers of medicines before distribution should conduct risk-based surveillance sampling. General guidelines for sampling pharmaceutical products can be found in the WHO sampling procedure for industrially manufactured pharmaceuticals (World Health Organization, 1990).

Medicine products to be sample-tested are selected according to a risk-based strategy by targeting those products with the greatest potential to harm the public health. These products, for example, may be imported from a new source that has no previous record of product quality. Samples of procured products should be retained even if they are not tested in case future problems arise.

Sampling criteria for quality control

Sampling should be performed by the MRA or by an organization that has appropriate authority. Sampling should follow standard operating procedures specific to the nature of the medicine, its source, and the size of the batch. A sampling form should be completed for each sample collected. MRAs should also sample finished dosage forms and bulk API material imported into the country.

A Three-Level Approach to Testing

Many developing countries do not have functional medicine quality control laboratories. Others have MQCLs that are either ill-equipped or understaffed, and subsequently, unable to test all medicines. On the other hand, full-scale pharmacopeial testing is expensive and can be performed only in well-equipped laboratories. Screening tests, which are less technically demanding than conventional tests, are useful for reducing the risks of distributing falsely labeled, spurious, or counterfeit products. This guide recommends applying a three-level testing approach for medicine quality control (Figure 8.1).

Level 1—Visual/physical inspection

External quality checks should be performed on every consignment. Visually inspecting the integrity of packs, appearance of tablets, or other dosing forms may help identify potentially substandard products. An examination of remaining shelf-life, compliance with approved labeling, packaging, and shipping instructions are also important.

The physical appearance of a medicine dosage form—shape, size, color—can provide an important clue in identifying suspicious and potentially counterfeit medicines, while a visual inspection may indicate tampering and non-uniform coloration. Visual inspection may also indicate substandard manufacture such as crumbling, chips, and cracks in solid dosage forms.

Visual and physical inspection of pharmaceutical products is the first step in any quality control program. Visual inspection helps assure the authenticity of the package. Medicine products from unusually cheap sources; products with missing or incorrect accompanying documentation; and products with defective packaging or with incomplete, damaged, or missing labels could easily be found just by careful visual inspection. To help inspectors identify these elements, they must understand the role and the importance of the product's package and label.

PACKAGING OF PHARMACEUTICAL PRODUCTS

Reviewing the various elements of a pharmaceutical product's packaging ensures that medicines arrive safely in the hands of the patients for whom they are prescribed. Packaging preserves the stability and quality of medicinal products and protects them against spoilage and tampering.

All medicinal products need to be protected, and therefore, packaged in containers that conform to prescribed standards, particularly with respect to excluding moisture and light, preventing leaching of extractable substances into the contents, and avoiding chemical interaction with the contents. The complexity of packaging materials and the highly technological nature of medicinal products confront manufacturers with significant problems. Neg-

ative interaction between packaging and drug products can occur because of the combination of diverse container components, active pharmaceutical ingredients, excipients, and solvents. Packaging must correctly identify the product. In addition, packaging quality must protect against all external influences that could alter the properties of the product—moisture, light, oxygen, and temperature; biological contamination; and physical damage.

The package must not have an adverse effect on the product, nor should the product have an adverse effect on the protective function of the packaging.

Pharmaceutical packaging materials and systems must be subject to the same quality assurance requirements as pharmaceutical products. A distinction must be made between primary and secondary packaging components. The primary packaging components—bottles, vials, closures (stoppers, caps, lids), blisters—are in direct physical contact with the product, whereas the secondary components—aluminum caps and cardboard boxes—are not. The choice of primary and secondary packaging materials depends on the degree of protection re-

Figure 8.1
Three-level testing approach in relation to location and purposes

Test level and location	Level of testing	Purpose of testing
Level 3 National/regional/ independent labs	**Complete testing** Pharmacopeial specifications	Determine drug quality according to pharmacopeial standards (pre- and post-shipment inspection
Level 2 Wholesaler, importer/ exporter, national programs, main warehouse, pharmacies	**Basic testing** Thin-layer chromatography, colorimetric methods, and disintegration	Check the identity of drugs and their approximate content (postmarketing surveillance)
Level 1 Dispensing level (health posts, rural retail outlets, consumers)	**Screening tests** Visual inspection of drugs, labeling, and packaging	Screen for detection of substandard/counterfeit medicines by inspecting for correct labeling/ packaging (before patient consumption)

quired, the compatibility with the contents, the filling method, user cost, presentation (in the case of over-the-counter drugs), and user convenience of the packaging—size, weight, method of opening and closing, and print legibility.

To ensure the efficacy of a product during its total shelf-life, pharmaceuticals must be regarded as a combination of the medicinal product and its packaging. During visual inspection, inspectors should verify that the package is appropriate for the drug contained within and ensure that the package protects the drug as indicated by the storage conditions. (See Storage and Distribution, Chapter 9.)

LABELS

All finished medicinal drug products should be identified by a specific label, as required by the national legislation, bearing at least the following information:

- Name of the product
- List of active ingredients, with International Nonproprietary Names and amount of all ingredients
- Dosage form and the number of dosage units, mass, or volume per package
- Batch or lot number assigned by the manufacturer
- Date of expiry in an uncoded form
- Special storage conditions or handling precautions that may be necessary
- Directions for use, and any warnings and precautions that may be necessary
- Name and address of the manufacturer, company, or person responsible for placing the product on the market.

Level 2—Screening tests or basic tests

The minimum tests recommended for screening purposes are the identity test and approximate content. For oral solid dosage forms, one may opt to conduct a simplified disintegration test. Some countries already use thin-layer chromatography (TLC) as an identification test, and a disintegration test for oral solid forms. Studies have proven that this level of testing could mean that an MQCL will test fewer samples. The screening tests for drugs to treat malaria and tuberculosis have been accepted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

THIN-LAYER CHROMATOGRAPHY

Thin-layer chromatography is a simple, flexible, and effective method for verifying the identity of a pharmaceutical product. TLC can be adapted to almost all drug types and can be performed in the field or in a laboratory.

A variety of chemical reagents, plates, equipment, and drug reference standards are required to perform TLC. Ready-to-use TLC kits are available from the German Pharma Health Fund e.V. Minilab (http://www.gphf.org/weben/start/index.htm).

DISINTEGRATION

A simple disintegration test checks whether uncoated, normal-release, solid-dosage forms will disintegrate within 30 minutes, which provides information about solubility. The notion is that a tablet that does not disintegrate will not dissolve. The testing medium is simply water

for common solid dosage forms or a diluted hydrochloric acid solution and a phosphate-buffer solution of pH 6.8 for enteric-coated tablets.

Level 3—Complete pharmacopeial testing

Level-three testing is performed only for the following types of products:

- Products that present any of the following problems: Physical signs of deterioration as detected by physical observation, unidentifiable origin, disputed analytical results, suspected adverse reactions, or potential evidence in litigation issues
- Products that are considered counterfeit. If a country does not have the resources to perform complete pharmacopeial testing, other options exist for doing so, such as using a WHO collaborating laboratory, or contracting with a certified/accredited private laboratory.[17]

Level-three testing is critical to medicine quality assurance, and requires a well-equipped laboratory and trained staff. Testing should be performed according to the quality specifications in the pharmacopeial monographs, using good-quality reference standards for the products to be tested. Monograph tests are performed to assure medicine quality, purity, strength, packaging, and labeling. For APIs, monographs usually require identity and purity tests, some physical tests that assure purity and identity (i.e., boiling point, melting point), and an assay. For dosage forms, monographs typically call for identity, purity, assay, dissolution for solid dosage forms, sterility for injections, bacterial endotoxins, pyrogen tests for infusions, and uniformity of dosage units.

The aims of third-level testing are as follows:

- To establish whether a given sample of a medicine manufactured locally or imported conforms to required specifications and whether packaging is adequate
- To examine pharmaceutical products suspected of being questionable in efficacy or safety, and to demonstrate and document any evidence of deterioration, contamination, or adulteration.
- To check the stability of products under local storage conditions.

The need may also exist to perform more comprehensive tests for products with the following concerns:

- Products show physical signs of instability or deterioration.
- Products are of unidentifiable origin.
- Products are sold by a supplier suspected of dealing in substandard products.
- Products have disputed analytical results.
- Products are suspected of causing adverse reactions.
- Products may be used as evidence in litigation.
- Products are provided through medicine donations.
- Products are suspected of containing certain impurities not mentioned in compendia specifications.
- Products do not contain the labeled active ingredients.

Box 8.1
Three types of quality control laboratories

Category	Description	Equipment required
1	Capable of conducting critical tests in the monographs: identity, assay, dissolution for solid dosage forms, and uniformity of dosage units.	■ Analytical balances, top-loading balance ■ pH meter ■ Thin-layer chromatography equipment ■ Centrifuge, desiccator, water bath, hot plates, vacuum pump ■ Manual polarimeter ■ Disintegration tester ■ Refractometer ■ Ultraviolet and infrared spectrophotometer ■ Drying oven and vacuum oven ■ Water distilling and water deionizer systems, basic ultrafiltration system, refrigerator ■ Dissolution tester (apparatuses 1 and 2, for tablets and capsules) ■ Karl-Fischer titrator ■ Instruments to perform high-performance liquid chromatography.
2	Able to perform the tests outlined in the monographs, including those requiring microbiological and biological tests.	All the equipment in the first category is needed plus the following: ■ Analytical microbalance ■ Refractometer, viscometer, friability tester ■ Gas chromatograph ■ Atomic absorption spectrophotometer ■ Equipped microbiological facility (autoclave, microscope, incubators, centrifuge, laminar flow hood, freezer) ■ Dissolution testers (all other apparatuses) ■ Melting-point apparatus ■ Polarimeter ■ Hardness tester ■ Friability tester ■ Viscosimeter
3	Able to address all scientific issues related to the efficacy and safety of all drugs, including studies related to the stability, bioequivalence, bioavailability, formulations, and method development.	As above, plus: ■ Infra-red spectrophotometry (IR)

In the absence of an MQCL

Having other facilities test medicines can be expensive and time-consuming, but the presence of an MQCL may deter those who manufacture, import, or sell counterfeit or poor-quality medicines. Countries are encouraged to establish their own MQCLs; all countries should have at least a Category 1 MQCL. The visual inspections of all drug consignments and the confirmation of at least the identity and the content of drugs must occur to assure the quality of essential medicines. Assuring the safety, efficacy, and quality of medicines in a country is an MRA's responsibility, whether or not it has an MQCL.

Other options for conducting medicine testing include the following:

- University laboratories, research laboratories, WHO collaborating laboratories (http://whqlily.who.int/)
- Regionally qualified medicines quality control laboratories
- Private laboratories.

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[17] WHO Collaborating Centres Related to Pharmaceuticals and Medicines, http://www.who.int/ medicines/information/infmedcollab.shtml.

CHAPTER 9

Maintaining Medicines Quality Through Storage and Distribution

Good medicine quality depends in part on proper storage and distribution practices. The goal of this chapter is to provide simple and useful guidelines for the optimal storage and distribution of medicines in an effort to maintain quality.

Guidelines for maintaining the quality of medicines can be adapted from the World Health Organization (2003c), the United States Pharmacopeia (2004), and other international pharmacopeia, and should complement, not replace, a nation's existing processes and procedures.

A checklist reviewing the steps to maintain medicine quality throughout the storage and distribution chain appears at the end of this chapter (Checklist 9.1).

Policy and Legal Framework

All persons involved in handling and distributing medicines should be familiar with the national and regional policies related to medicines. National medicines policies should identify participants—pharmaceutical manufacturers, importers, wholesalers, retailers, pharmacies, and health professionals—and their roles in complying with regulations that govern the following issues:

- Production and importation
- Warehousing and distribution
- Prescription drugs
- Over-the-counter drugs
- Dangerous and controlled substances (narcotics, psychotropic drugs, etc.)
- Quality control and quality assurance: Registration, licensing, inspection, monitoring, and evaluation

- Personnel training (personal hygiene, sanitation, and proper use of protective clothing).

Table 9.1 shows storage and distribution practices for maintaining minimum levels of quality assurance and quality control as explained in this chapter.

Storage

Good storage practices involve more than adequate facilities. Equally important are procedures for receiving, labeling, inventory, and security (Box 9.1).

Security and safety

Only authorized personnel with proper identification should have access to locked storage areas. Each storage site should have an adequate number of qualified and certified personnel to perform quality assurance functions.

Table 9.1 Minimum QA/QC storage and distribution practices

Receive Incoming Goods	Storage	Dispatch/Delivery	Transportation
1. Follow SOP for receiving goods, including checking for completeness, accuracy, and validity of documents. **2.** Quarantine.[a] **3.** Perform visual/physical inspection for name of drug, strength, dosage form, quantity, labeling, and packaging. **4.** Take suspected or random samples to lab for testing. **5.** Record any damages and discrepancies. **6.** Report the damages and discrepancies to the manager and communicate with suppliers, if necessary.[b]	**1.** Follow SOP for good storage practice. **2.** Check temperature, humidity, and ventilation. **3.** Place each drug in its designated space. **4.** Update stock card or product register.	**1.** Follow SOP for dispatching goods, including checking for completeness, accuracy, and validity of documents. **2.** Perform visual inspections for name of drug, strength, dosage form, quantity, labeling, and packaging.	**1.** Follow SOP for dispatching goods, including checking for completeness, accuracy, and validity of documents. **2.** Pay attention to mode of transport, transport conditions (i.e., temperature and humidity), and transport duration. **3.** Pay attention to products requiring low temperature.

SOP = standard operating procedure.
a. All incoming shipments must be quarantined until the receiving report is cleared by authorized personnel for release into their allocated storage positions.
b. All recall products must be in separate quarantine rooms while awaiting instructions from the responsible regulatory authority.

Box 9.1 Key points of good storage practices

- Limit access to storage areas to authorized personnel only.
- Ensure proper storage conditions (temperature, humidity, lighting).
- Storage areas should be well organized and clearly labeled.
- Expiry date should be clearly labeled on all containers.
- Products should be arranged by FEFO and FIFO.
- Perform regular inventories of pharmaceutical materials and products.
- Maintain and update records of all materials in storage.

Security protocols for entering storage areas should involve at least two levels of clearance to minimize the likelihood of unauthorized entrance (e.g., multiple locks controlled by multiple staff members).

Storage areas should have clearly marked fire exits, and all personnel should be familiar with their locations. Check smoke detectors monthly. Fire extinguishers and fire alarms should be visible and accessible, and someone should be trained to administer first aid, when necessary.

Storage areas

When selecting a storage location, account for the amount of space required, transport accessibility and convenience, and security. Storage areas should have adequate lighting, ventilation, and protection from adverse weather conditions. Pharmaceutical products should be stored off the floor and suitably spaced to permit cleaning and inspection. The floor and surfaces of storage areas should be covered by tiles or other materials that can be easily cleaned. Storage areas should have an adequate number of clearly labeled shelves, and there must be easy access to products stored on top shelves.

Well-organized storage areas, with separate areas for storing different categories of materials and products—packaging materials; intermediates; raw and finished products; products in quarantine; and released, rejected, returned, or recalled products—are essential.

Finally, a sanitation program should be in place to maintain cleanliness. Care must be taken during the cleaning process to avoid contaminating the pharmaceutical products. Some important considerations for cleaning storage areas include:

- Perform cleaning on a weekly basis, or more often based on the facility's activities.
- Avoid sweeping with brooms because they tend to create airborne dust; a dust mop is preferable.
- Follow dusting by mopping with soapy water or disinfectant.
- Avoid direct contact of cleaning solution with storage containers.

Storage conditions

Storage conditions should be monitored and recorded weekly or, if possible, daily. Equipment used for monitoring storage conditions—thermometer and hygrometer—should be calibrated at defined intervals.

Table 9.2 Recommended storage conditions according to specific labels

Storage Label	Recommended Storage Condition
Store between 2°C and 8°C	Refrigerate; don't freeze
Store below 8°C	Refrigerate
Store between −5°C and −20°C	Freeze
Store below −18°C	Deep freeze

Source: World Health Organization, 1996a.

All necessary precautions should be taken to minimize the effect of adverse external conditions on the quality and stability of drug products. This is especially important for products requiring low-temperature storage. In most cases, drug products should be stored under normal storage conditions: dry, well-ventilated premises at temperatures of 15°C to 25°C or, depending on climatic conditions, up to 30°C. Extraneous odors, other indications of contamination, and intense light must be excluded.

Medicines require appropriate storage instructions. Unless specifically stated, temperature deviation may be tolerated only for a short time, such as during local transport. Table 9.1 offers recommended storage conditions according to label requirements.

Cold storage

Household refrigerators are not suitable for storing medicine products because they lack the precise electronic control necessary to maintain a typical temperature range of between 2°C and 8°C. Commercially available refrigerators designed for medicine products should be used instead. Monitor temperature with a thermometer that has an accuracy rate of ±0.5°C.

Here are two general storage rules to follow (also see Table 9.2):

- Products sensitive to temperatures above 8°C should not be stored near the door.
- Products susceptible to temperatures below 2°C should not be placed in the airflow of the refrigeration unit.

Documentation of records

Written records of all storage area activities should be well maintained and easily accessible, including the handling of expired materials or products. These should adequately describe the storage procedures and the path of origin of pharmaceutical products, in case a product must be recalled. Permanent written or electronic information should exist for each stored material or product. The information should clearly indicate recommended storage conditions, any necessary precautions, and retest dates.

Delivery records should be kept, including a description of the products, their quality as described on the label, quantity, supplier, supplier's batch number, the date of receipt, assigned batch number, and the expiry date. These records should be retained for at least the shelf-life of the product.

Comprehensive records should be maintained showing all receipts and issues of pharmaceutical products according to a specified system (i.e., by batch number).

Material safety datasheets should be displayed and clearly visible in storage areas. These can be obtained from most medicine manufacturers.

Labeling and containers

Proper containers should be used to store all pharmaceutical products to avoid contamination. All finished medicine products should have labels, including dosage form and strength.

All containers should be clearly labeled with at least:

- Name of the material
- Batch number
- Arrival or receipt date
- Expiry or retest date
- Specified storage conditions
- Reference to the pharmacopoeia, where applicable.

Inventory

An inventory software program is the most efficient method for controlling inventory management.[18] However, a monthly inventory check can be performed with a simple spreadsheet to compare actual and recorded items. All inventory discrepancies should be investigated for inadvertent mix-ups or incorrect issue.

In manufacturing facilities, partially used containers of materials and pharmaceutical products should be securely closed and resealed to prevent spoilage and contamination during subsequent storage. Pharmaceutical products from containers that have been opened or partly used should be finished before opening a new container.

Damaged containers should not be issued unless the quality of the material has been shown to be unaffected. All damaged containers should be replaced by new containers.

Stock rotation and control

Sensitive and hazardous materials—radioactive products, narcotics, and combustible liquids—should be stored in a contained area. Handling of controlled substances, such as narcotics, should follow regional or national laws related to dispensing prescriptions, licensing, personnel, and warehouse inspection. Materials and pharmaceutical products should be handled and stored to prevent contamination, mix-ups, and cross-contamination. Stock should be appropriately rotated. The first expiry/first out (FEFO) and first in/first out (FIFO) principles should be followed.

Expired, rejected, and recalled drugs

All stocks should be checked regularly for expired materials and pharmaceutical products, which should be removed as soon as possible. Expired or rejected products should be identified and controlled under a quarantine system designed to prevent use until a final decision is made regarding their fate.

Broken or damaged items should be separated and withdrawn immediately from usable stock. Returned goods, including recalled items, should be handled by approved procedures according to regional or national regulations. All returned goods should be destroyed or placed in quarantine, only to be returned to storage after a satisfactory quality reevaluation.

Any reissued stock should be identified and recorded in stock records. Records of all returned and recalled goods should be maintained.

Receipt of incoming materials and pharmaceutical products

Comprehensive records should be maintained for all receipts and issues of materials, according to a specified system (e.g., by batch number). The following should occur at the time of receipt:

- Goods should match the relevant purchase order and each container should be labeled with batch number, type of material or pharmaceutical product, and quantity.
- Container uniformity should be checked and subdivided according to the supplier's batch number, should the delivery comprise more than one batch.
- Each container should be inspected for contamination, tampering, and damage. Suspect containers should be quarantined for further investigation. The quarantine should remain in effect—in a separate area—until an authorized release or rejection is obtained.

Distribution

The quality assurance component of distribution includes receipt of procured medicines at the port of entry, clearance through customs, and transportation from a central warehouse to depots and health facilities where they are stored and dispensed to patients. For locally produced drugs, distribution starts when products are dispatched from the manufacturer's warehouses. The distribution process should be well controlled and tracked, with registers and signed transfer documents (Box 9.2).

Box 9.2 Key points of distribution practices

- Rapid clearance through customs avoids storage condition deterioration and fees.
- Medicines must be inspected for quality and quantity before distribution.
- Maintain proper storage conditions (temperature, humidity, etc.) during transport.
- Verify and document delivery orders.
- Check the integrity of packaging when drugs arrive.
- Clearly label containers.
- Maintain delivery records.
- Provide easy access to delivery records.

Dispatch and delivery

Pharmaceutical products should be transported in a way that maintains their quality and meets their storage requirements. The outside container should offer adequate protection from all external influence and should be indelibly and clearly labeled.

Dispatch and transport of pharmaceutical products should occur only after a request or purchase order is received and approved. Dispatch procedures should account for the nature of the pharmaceutical products and any special precautions that might be required.

Dispatch records should include the date of dispatch; the customer's name and address, including facsimile and telephone numbers; product description—name, dosage form and strength, batch number, and quantity; and transport and storage conditions.

Transport

During transport, the mode of transportation, destination, and transport duration must be taken into account to ensure the integrity of the medicines. The two most important factors are temperature and humidity, which need to be continually monitored and recorded.

Extra attention should be paid to transporting products requiring low-temperature storage, taking environmental and seasonal changes into consideration.

Insulated packaging without cooling elements may provide adequate protection for small-volume deliveries that require a short transit time (<3 hours). Larger deliveries requiring longer transit time should be transported in proper cooling environments. When using dry ice (solid CO_2), measures must to taken to make sure the ice does not directly contact the products, as extremely cold temperature might affect the integrity of the product.

Product recalls

There should be a standard operating procedure to promptly and effectively recall pharmaceutical products and materials known or suspected to be defective:

- Products being recalled should be easily traced by batch number.
- Recalls should be classified according to the level of risk to the consumer—mild or serious illness, death, or no adverse clinical effect.
- After a recall has been issued, progress should be monitored to ensure complete compliance with regulatory requirements.
- The supplier should be notified of the recall in writing and be required to replace defective products. The purchaser may consider withholding payment until defective products are replaced.

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[18] Two examples of inventory software programs are INVEC-2, developed by Management Sciences for Health, 4301 N. Fairfax Drive, Suite 400, Arlington, VA 22203 USA; and SWEDIS, from Pharmasoft Swedis AB, P.O. Box 1237, S-75142, Uppsala, Sweden.

Checklist 9.1
Maintaining quality of medicines through storage and distribution

POLICIES AND GUIDELINES

☐ Apply guidelines for storing and distributing medicines from storage facilities.

WAREHOUSE PREMISES

☐ Premises should be approved by a relevant governing authority and should exhibit the following parameters:

- Adequate lighting and ventilation
- Smooth and clean walls and floors
- Floor in good condition, dry, with no stagnant water
- Equipped with secured doors.

PERSONNEL

☐ Employ adequately trained personnel to manage the warehouse.

☐ Use adequate personal protective garments at all times.

☐ For a small warehouse, fewer staff may perform the following functions; but for a medium-size warehouse, personnel should include:

- One manager, preferably a pharmacist with accounting skills
- One pharmacist or pharmacy assistant, at least, with experience in quality assurance/quality control
- One pharmacist or one pharmacy assistant to manage inventory control
- One pharmacy assistant or equivalent to manage receiving and dispensing
- Support personnel, such as forklift drivers.

MANAGEMENT AND OPERATION

☐ Apply strict standard operating procedures for handling, storing, and distributing medicines as described in Table 9.1.

☐ Obtain feedback from clients about operations and services.

☐ Enforce adequate standard operating procedures to enable staff to perform their work.

- Conduct physical inspections of incoming and dispatching goods, checking that the right medicine matches the order.
- Perform quarantine and basic testing before storage and dispatching.

☐ Maintain records of medicines received and distributed for at least three years or in accordance with the regulatory requirements that can be retrieved at any time.

☐ Follow First In/First Out and First Expiry/First Out principles and practices.

☐ Ensure that at least 80 percent of transportation vehicles are in good working condition (if transportation is not contracted) to ensure delivery time is kept to a minimum.

☐ Do not delay port clearance for more than one week.

☐ Have direct access to an overseas telephone line to which managers of warehouse, import department, and quality assurance/quality control have access.

STORAGE

- ☐ Keep drug storage areas well ventilated and clean at all times.
- ☐ Use adequate shelves, racks, pallets, and trucks for appropriate storage, handling, and dispatching.
- ☐ Employ an effective system to notify when medicines will expire, and adequately handle these products.
- ☐ Maintain temperature- and humidity-monitoring equipment or instruments in good working order.
- ☐ Have cold, cool, and special rooms for dangerous, poisonous, and volatile substances and medicines.
- ☐ Do not issue any product until the previous day's records have been updated.

CHAPTER 10

Managing Medicines Quality at the Dispensing Level

Previous chapters discussed the roles and responsibilities that manufacturers, national regulatory agencies, procurement agencies, and logistics and distribution services play in producing and providing high-quality medicines. The last step in the process of providing high-quality medicines to patients requires rational prescribing practices, good dispensing procedures, and patient adherence.

The purpose of this chapter is to provide people who dispense medications with guidance on preserving and monitoring the quality of drug products and to identify specific actions they can take to ensure that appropriate medicines of good quality are properly dispensed and used. Inappropriate prescribing and dispensing practices can directly or indirectly jeopardize the quality of patient care and negatively influence treatment.

Role and Responsibilities of Dispensers

Dispensing is often considered to be simple and routine, with little room for error. The significant investment made in ensuring product quality up to the point of dispensing may be wasted if the correct drug in the right form is not delivered to the right patient, in the prescribed dosage and quality, with clear instructions, and in an appropriate package that preserves the medicine's potency (Management Sciences for Health, 1997; p. 484).

The traditional role and responsibility of a dispenser focuses on six major activities:

1. Maintaining a proper dispensing environment
2. Receiving and verifying medicines
3. Receiving, confirming, and understanding prescriptions
4. Preparing medications for dispensing

5. Recording the actions taken
6. Issuing medications to patients with clear instructions and advice (Management Sciences for Health, 1997; p. 486).

Maintaining a proper dispensing environment

The dispensing environment should be clean and organized, exhibiting the characteristics described below.

Building layout. The building housing the medicine outlet should be a spacious, permanent structure, with an efficient working area to allow free movement of staff.

Scheduled cleaning. Dust and dirt can contaminate medicines. Floors, shelving storage, and working surfaces should be cleaned daily.

Dispensing equipment. Adequate equipment, such as tablet counters and balances, ensures accuracy when medicines are prepared for dispensing.

Scheduled equipment cleaning. Dispensing equipment must be cleaned after every use and at the end of the day to avoid possible cross-contamination of medicines.

Staff hygiene. Dispensing personnel must practice good personal hygiene to avoid product contamination.

Organized workplace. Medicines should be organized logically and in accurately labeled containers to minimize the risk of choosing the wrong medicine unintentionally. Shelves should be organized according to dosage forms in tablets, capsules, syrup, and mixture, and arranged in alphabetical order for easy access.

Inventory rotation system. To avoid product loss from expiry, an inventory rotation system, such as First Expiry/First Out and First In/First Out, ensures that drug quality is monitored and maintained at all times.

Proper record maintenance. Accurate and up-to-date records must be retained for all products issued in compliance with national regulations. A list of available medicines should be updated daily so that prescribers know which medicines can be used.

Proper staff scheduling. Work should be scheduled to ensure there is adequate staff coverage during peak demand hours.

Proper storage conditions. Products should be stored as close as possible to their recommended storage conditions—temperature range, light exposure restrictions, closed containers, etc.—to maintain product quality (Management Sciences for Health, 1997; p. 485).

Receiving and verifying medicines

When medicines arrive at the dispensary, staff are responsible for making sure that the product conforms to the product they ordered and that it is in good condition.

The product label and packaging information should be visually inspected to verify the product name, dosage form, strength, batch or lot number, date of manufacture, expiry date, and manufacturer's name and address. The product quantity should be confirmed as correct (World Health Organization, 1996a). The package should be visually inspected for damage and proper sealing.

Visually inspect the product for discoloration, deterioration, and physical degradation, and damage.

If damage is discovered, the staff should record and report the information to the purchasing personnel, who will resolve the issue with the supplier. Damaged products need to be disposed of according to standard operating procedures.

Receiving, confirming, and understanding prescriptions

When a prescription is received, dispensing staff should take the following actions to ensure the patient receives the appropriate medication in the correct quantity:

- Read the prescription to confirm the patient's name and address.
- Interpret any abbreviations written by the prescriber.
- Confirm that the prescribed dosage is within the acceptable range for the patient (considering the patient's age and gender).
- Calculate and confirm the dosage and quantity of medication, and issue the required quantity.
- Determine whether the potential for drug-drug interaction exists and notify the patient of such (Management Sciences for Health, 1997; p. 487).

Preparing medicines for dispensing

Proper drug preparation practices must be followed. The points described below outline standard drug preparation practices.

Select the product storage container. The container label should be read and the medicine name and dosage strength cross-checked against the prescription.

Measure and count products. Counting products to confirm quantity should always occur on a clean, dust-free surface. Options for counting include a triangular tablet counter, a sheet of paper and a knife, or pan weighing scales. A dispenser's hands should never directly contact the product to avoid product contamination. Liquids must be measured in clean, well-labeled containers with tight-fitting covers and should be poured from the stock bottle, with the label kept upward, to avoid damaging the label with spilled liquid.

Reseal the storage container. Once the product has been measured or counted, the storage container should be closed, as exposure to air gradually diminishes medicine quality. After closing the container, the label should be rechecked for the medicine's name and strength.

Pack the product. A suitable container will preserve the quality of the product until a patient uses the medicine. Tablets and capsules should be packed in clean, dry containers such as bottles or plastic envelopes. Liquid preparations should be dispensed in pharmaceutical bottles to distinguish them from nonpharmaceutical preparations such as food and drinks.

Label the product. The label should include information about the brand name and generic names; strength, dose, frequency, and duration of use; dispensing date; patient name; supplier name and address; and child safety warning.

Double-check the preparation against prescription and storage container. Another dispensing staff member should double-check the preparation against the prescription and its storage container (Management Sciences for Health, 1997; p. 489).

Recording the actions taken

For inventory tracking purposes records of products dispensed must be maintained. This is helpful if a need ever arises to contact a patient regarding a problem with the medication. Key information to record includes the patient's name, age, and contact details; name and strength of the medicine dispensed; total amount dispensed; date dispensed; and the names of both the persons who prescribed and dispensed the medication.

Issuing medicines with clear instructions and advice

Patients must be able to comply with the instructions on the prescription package. They should know what the medicine treats; the dosage, frequency of use, and length of treatment; when to take the medicine; how to take the medicine; and how to store and care for the medicine (i.e., use-by date) (Management Sciences for Health, 1997; p. 489).

The person who dispenses the medicine should always strive to confirm that the patient clearly understands the instructions for taking the prescription.

Requirements in Basic Dispensing Functions

Appropriate training

Medicine dispensing is traditionally performed by a trained and licensed pharmacist. Shortages of trained pharmacists, however, will often result in dispensing being performed by other health care providers. These individuals require training that is appropriate for the range and complexity of medicines they dispense. Individuals other than licensed pharmacists who dispense medications must have the following knowledge:

- Common uses, dosage, side effects, drug-drug interactions, and storage requirements for medicines being dispensed
- Good calculation skills
- Ability to assess the quality of preparations
- Good hygiene
- Ability to communicate effectively with patients (Management Sciences for Health, p. 486).

Standard operating procedures for proper storage, handling, and monitoring of medicines

Dispensing outlets are advised to establish standard operating procedures that identify practical actions for dispensers to take to ensure that medicines are stored and handled properly. All dispensing activities should be recorded to certify appropriate monitoring of drug usage. For details on storage of medicines, see Chapter 9, Maintaining Quality Through Storage and Distribution.

Strengthening good dispensing practices

Besides having effective medicine laws, additional methods will encourage adherence to good dispensing practices. Some of these are discussed here.

- Professional bodies are encouraged to promote the use of good dispensing practices guidelines such as the Good Pharmacy Practice in Developing Countries from the International Pharmaceutical Federation (1998).
- Empowering and cultivating confidence in dispensers can be ensured by their representation on national health boards and by recognizing dispensers as team players in matters related to the success of the entire health delivery chain.
- Providing continuous education and training for dispensers, especially in areas related to customer care, counseling, and reporting of adverse drug reactions will ensure good dispensing practices.
- Providing adequate and appropriate dispensing materials, such as dispensing trays, drug envelopes, dispensing cups, spoons, bottles, and jars will make a dispenser's work easier and practical, minimize mistakes, and instill confidence and pride.
- Establishing a quality award to be given to the best dispensing outlet will encourage all dispensers to use good pharmacy practices.

Checklist 10.1
Managing medicines quality at the dispensing level

DISPENSING PREMISES

☐ Approved by a relevant governing authority.
- ☐ Premises have adequate lighting and ventilation.
- ☐ Adequate security installed to prevent break-in and theft.
- ☐ Walls and floors are smooth and clean.
- ☐ Floors are in good condition, dry, with no stagnant water.
- ☐ Premises have adequate lavatory facilities, including running water and a hand drier to promote personal safety and hygiene.
- ☐ Premises are conducive to effective communication between the dispenser and the patient, and ensure sufficient privacy.

PERSONNEL

☐ Employ adequately trained personnel to serve patients.

☐ Use adequate personal protective garments at all times.

☐ Attend dispensary training programs to enhance job skills and experience.

MANAGEMENT

☐ A pharmacist or pharmacy technician should manage the dispensary of medicines.

☐ Apply strict standard operating procedures for handling and dispensing medicines.

☐ Obtain feedback from patients and the general public about operations and service.

☐ Encourage good work and maintain quality in dispensing through an award system.

OPERATION

☐ Ensure the presence of at least one pharmacy technician in the dispensary at all times.

☐ Enforce adequate standard operating procedures to enable staff to perform their work.
- ☐ Confirm the correct medicines are dispensed (against the prescription or order) in the right dosage form, strength, quantity, packaging, and labeling—to the right patient.
- ☐ Perform physical quality inspection of the medicines before dispensing.

☐ Maintain records of medicines issued for at least three years or in accordance with the regulatory requirements that can be retrieved at any time.

☐ Follow First In/First Out and First Expiry/First Out principles and practices.

☐ Evaluate whether patients understand how to take the medicines they have been prescribed.

STORAGE

☐ Keep drug storage areas clean and well-ventilated at all times.

☐ Use adequate shelves, plates, and pallets for appropriate storage, handling, and dispensing.

☐ Maintain appropriate storage area temperatures and humidity.

☐ Employ a system of notification for when medicines are about to expire.

CHAPTER 11

Medicines Information

A medicine or drug can be defined as "the active substance or chemical contained within the drug plus the information." The concept of this definition places equal importance on both the active substance and the information that should be provided with it. The misuse or irrational use of medications in many countries—often due to the lack of an unbiased source of information for drug prescribers or consumers—poses serious health problems, resulting in less effective therapy, disability, and even death. In addition to these consequences, inappropriate use of medicines further depletes already scarce resources.

Irrational or inappropriate use of medicines is a common problem, especially in developing countries. Many experts suggest that 30 percent to 60 percent of primary health care patients receive antibiotics, perhaps twice the rate clinically necessary. A technical review by the United States Pharmacopeia of antimicrobial drug information in six countries found that information on proper indications, dosage, precautions, and side effects was typically lacking (Rational Pharmaceutical Management Project, 2000). Other problems include the overuse of injections, the unnecessary prescription of multiple medicines for one indication, and the use of combination drugs that are more costly and have no advantage over single compounds.

Although information alone may not change prescribing patterns, any type of intervention designed to improve clinical medicine use must include good medicines information. Clinicians need a regular source of up-to-date, high-quality information to make optimal treatment decisions. Governments need to communicate to the public why mechanisms such as a national formulary or essential medicines list exist (i.e., why one medicine is included on the list and not another).

Thus, medicines information is an essential element in achieving national health goals, and should ideally be a part of comprehensive national medicines policies and plans. The consequences of not having a system that provides objective information are the wasteful use of resources and irrational prescribing, which undermine many health services, particularly in the developing world.

Improving Access to Medicines Information in Developing Countries

Above all, national governments need appropriate medicines policies. Physicians, dispensers, and the public should have a guaranteed availability of unbiased information. This must be the base for registration and should be a basic requirement for approval and marketing of a medicine.

Also needed is a sound system for adverse event monitoring. There clearly has to be a mechanism at the national level to disseminate new, critical information. When a new, serious adverse reaction is reported for a drug available in the country, health care professionals and consumers need to have access to that information as quickly as possible. Dissemination of this information must be a national government responsibility.

Limits need to be placed on advertising and promotion, and these limits need to be enforced. Health care professionals and consumers need assurance that what is being promoted is effective, and that what is being said about the product is truthful. There must be a commitment to the public's health at the national level.

Medicines Information Centers and Networks

A medicines information center is an institution dedicated to providing objective, accurate, and up-to-date information about medicines and their use, and which is able to communicate a better understanding of medicines to various categories of users for the ultimate benefit of the patient.

The primary role of a medicines information center in a developing country is to provide clear and definitive information on well-established essential medicines and to promote their rational use. A secondary role is to maintain current pharmacological and therapeutic literature, and to disseminate relevant information as it becomes available.

A medicines information center's objectives could include one or many of the following points:

- To provide information to health professionals on specific problems related to the use of medicines in particular patients
- To provide information to officials in government agencies to optimize the decision-making process
- To prepare and distribute material on medicines to health care personnel in the form of a medicines information bulletin or other media
- To prepare and develop guidelines and formularies
- To improve patient compliance and to provide a guide to responsible self-medication
- To develop and participate in continuing education programs
- To participate in undergraduate and graduate teaching programs
- To develop educational activities regarding the appropriate use of medicines for patients in the community
- To develop and participate in research programs.

Standard of good-quality medicines information

The standards for a chemical or active drug substance have been well understood and well supported for many years. Familiar issues such as good manufacturing practice are the mainstays of the manufacturing process.

It follows that standards exist for the provision of good-quality medicines information. The information provided should be: objective, independent, scientifically validated, evidence-based, and up-to-date.

Planning and setting up a medicines information center

Although medicines information centers may be located in a variety of places, their location is closely related to their immediate objectives and their target populations. Experience in the United States has demonstrated that most medicines information centers are established in teaching hospitals. Location in a hospital offers certain advantages because it:

- Facilitates the development of responsive information activities, a fundamental objective of any MIC.
- Encourages direct interaction with health professionals, primarily drug prescribers.
- Provides better access to high-risk groups that could benefit from patient educational programs.
- Provides a better opportunity for immediate solutions to medicines-related cases.

The Ministry of Health is an ideal site when the objectives of the center are (1) to provide information to support the registration of medicines or national drug control programs, and (2) to advise policy decision-makers.

Medicines information centers can also be established in allied health schools, or more specifically, in schools of medicine. In these cases, the primary objective of the center is to support the training of health professionals, not only with regard to pharmacotherapeutics, but also in the management of information sources. Professional associations and guilds may also be appropriate for setting up MICs with objectives to update drug dispensers in the rational use of medicines, and to educate consumers.

Medicines information centers must have a specific room set aside for the purposes of providing information about medicines; at least one dedicated and appropriately trained staff member who answers queries; the appropriate resources for answering queries received by the unit (Box 11.1). The MIC must document the queries received and answers provided.

Box 11.1 MIC equipment requirements

An MIC needs an office with access to the following:

- Photocopy machine
- Fax
- Telephone
- Answering machine
- Computer
- Internet
- Printer
- Library of resources

Medicines information centers must actively promote their services. This is particularly important when such a service starts; many practitioners and members of the public will find an MIC a new concept.

Medicines information centers should develop a set of minimum standards to ensure that performance of information services is continuously maintained at a high standard. Quality assurance is valuable because it facilitates the identification and the correction of any possible deficiencies in knowledge, skills, and technologies. Ideally, it should cover all aspects of the MIC's activities.

Process indicators are used to reflect the level of activity in a center and help maintain quality assurance. Process indicators give some idea of the value placed on the center by its users (Box 11.2).

Box 11.2 MIC process indicators

- Average number of inquiries answered per month
- Percentage of inquiries that need to be referred to another level of expertise
- Average time taken to answer an inquiry (verbal/written response)
- Categories of information requested
- Type of inquirer using the center
- Type and number of publications produced by the center per year
- Readership (circulation) of its publications
- Number of in-service training programs per year
- Number of external training programs attended by staff per year
- Number of educational programs provided by the center per year
- Number of presentation/lectures delivered per year
- Number of articles/papers published per year
- Number and type of research projects completed
- Number of adverse drug reaction reports per year

Financial support

It is essential that a medicines information unit have access to neutral, independent, and autonomous resources. It is essential that financial support be free of any bias, such as pharmaceutical industry support.

The financing of an MIC is an essential element for its establishment and operation. The decision to establish an MIC should not be based solely on the availability of external sources of funds. Medicines information centers should be built on a cooperative model, utilizing existing resources to the greatest extent possible. Governmental resources are a suitable source of financial support for drug information services considered to be in the public domain, provided that the authorities respect the neutral, independent, and autonomous nature of the MIC functions.

Financial planning is a crucial first step in establishing a successful MIC. Detailed budgets should be prepared that reflect the objectives, the services to be offered, and the implementation of these over time. All MICs need to have a fixed operational budget. The operational expenses include funds to cover costs of utilities, such as electrical power and telephone services, permanent updating of the information sources, and the salaries of the personnel who work in the center. Another important portion of the budget should be devoted to the maintenance of equipment, such as the computer system, copier, fax, and telephone. Annual budgets in a strategic plan provide evidence that the center will be sustainable and will be managed soundly. Budgets must contain both capital costs and operational costs (Box 11.3).

A funding strategy will depend on the nature of the services to be offered, as well as the type and size of the target group. In the context of each country's realities, funding for an MIC may come from government, professional associations, university or other training institutions, nongovernmental organizations, or a coalition of several of these groups. Regardless of financing, the independent nature of the services an MIC provides should never be threatened. No institution or group should be able to influence what information is or is not offered. Sources of funding can be from several organizations; however, in this case, the neutrality and independence of the services cannot be compromised. Funding from pharmaceutical companies should be avoided.

Where capacity for pharmaceutical registration exists, a small percentage of the fee could be allocated to finance a national MIC. Countries with national medicines policies and essential medicines programs can easily integrate the medicines information system into their overall plans and allocate resources for it.

To minimize the cost of operating the MIC, publishers could be asked for complimentary copies of reference materials. Book donation schemes exist and international development agencies sometimes provide grants for the purchase of didactic materials.

Sustainability is more likely if MIC services, such as formulary development or medicines utilization review programs, become recognized as important to the institutions housing the centers.

Box 11.3 Financing an MIC

CAPITAL COSTS

- Personnel resources—selection and training
- Equipment
- Furniture and office space
- References sources, databases

OPERATIONAL COSTS

- Salaries (staff and outside support)
- Ongoing staff training and education
- Maintenance, replacement costs, and recurrent costs of office space
- Telephone and postage
- Stationery and photocopying costs
- Computer updating
- Subscription costs for books, journals, compact discs, and so on

One of the most realistic ways to obtain funds is through the support of donors. MICs are encouraged to seek grants from international organizations for funding and special projects.

Medicines information centers can also consider charging for services without compromising the objectives of the center and considering the specific target population to which the information is directed. These factors should always be analyzed before charging a fee. It is recommended, however, that the MIC should provide free services initially as a strategy for creating demand.

CHAPTER 12

Rapid Assessment of Medicines Quality Assurance and Medicines Quality Control

Problems related to the quality and safety of medicines are becoming an increasing concern in many places around the world, especially in developing countries. Adequate medicines legislation and regulations, competent medicines regulatory authority (MRA), and appropriate medicine information are required to ensure the safety, efficacy, and high quality of medicines.

Legal structures are the foundation of medicines regulation. In some countries, medicines laws may not cover certain aspects of pharmaceutical activity. For example, the production of certain medicines for domestic use may not require compliance to good manufacturing practices or clinical study data may not be mandatory requirements for medicines registration. Many MRAs do not provide documented standard procedures for registration; others do not have written guidelines and checklists for inspection. All this has resulted, among other things, in a regulatory gap and inconsistent enforcement of laws, which often leads to less clarity and a lack of coherence in the medicines regulatory process.

All medicines regulatory authority functions must work in concert in order to provide effective public health protection. Key functions are licensing, product quality assessment and registration, inspection of manufacturing facilities and supply channels, laboratory control, and post-marketing surveillance for quality, adverse drug reactions, and control of promotion and advertisement of pharmaceuticals.

Objectives of the Assessment

The objectives of assessing a country's medicines quality assurance and control are:

- To determine whether or not a functional and operational MRA exists in country
- To examine what approaches and mechanisms the country uses to ensure the quality of pharmaceuticals sold there and, if an MRA exists, how it carries out its responsibilities
- To identify strengths and weaknesses of the country's medicines QA program and quality control (QC) systems and the reasons for them
- To make suggestions and, where appropriate, recommendations to policymakers, decision-makers, and authorities responsible for designing and developing appropriate medicines QA/QC systems adaptable to their political and socioeconomic conditions.

Methodology

Methodological framework

The methodology of this assessment is based on the following framework (see Figure 12.1):

Premarketing quality assessment, which includes the assessment of medicinal drug product quality, safety, and efficacy for registration or market authorization.

Regulatory functions, which cover central administration (allowing the functioning of a regulatory authority), quality control or testing, inspection services, licensing of persons and pharmaceutical establishments, and product recall.

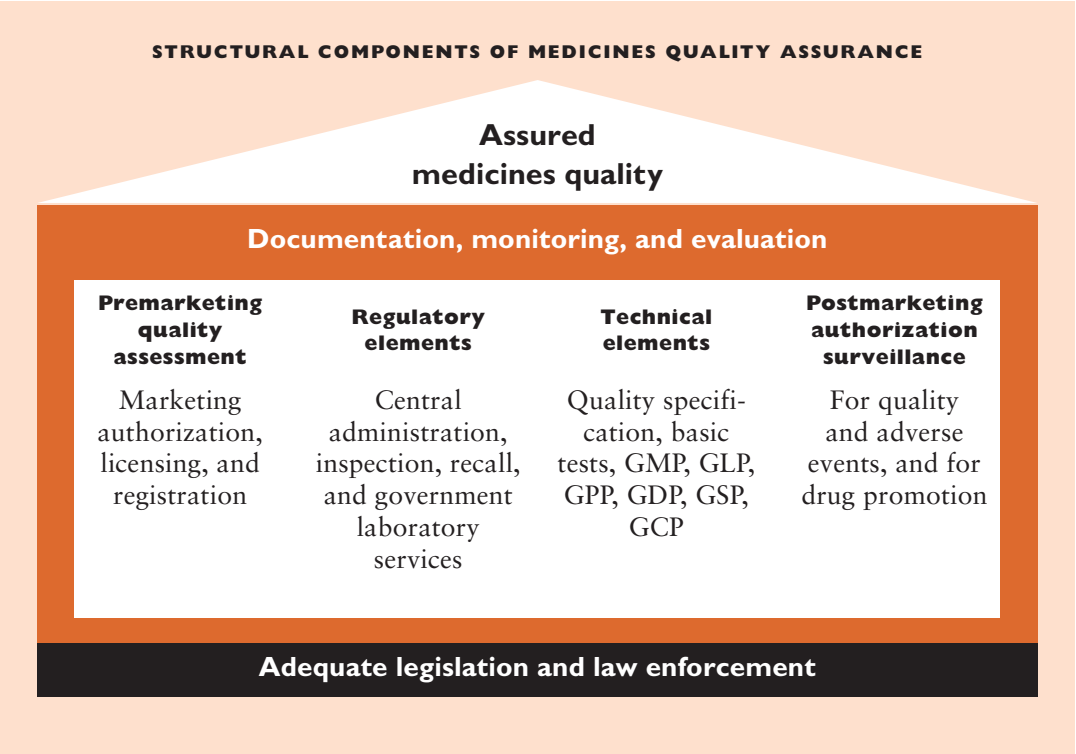

Figure 12.1
Key components of a medicines quality assurance plan

Technical elements, which address norms, standards, specifications and procedures, and good practices.

Postmarketing surveillance, which covers monitoring for medicine quality and adverse reactions, and control of medicine promotion and advertising.

Figure 12.1 also illustrates the framework for data collection and the focus areas for assessment of the structural components of medicine quality assurance.

Assessment process

The process through which a nation's MRA can develop a medicines quality assurance program and quality control system has four steps.

1. Planning for assessment
2. Data collection
3. Data analysis
4. Reporting and recommendations.

PLANNING FOR ASSESSMENT IN THREE STEPS

1. Set up an Assessment Team or Working Group. The planning usually starts with establishment of an independent assessment team or assessment working group with defined role and scope of work. The team should consist of a team leader and two experienced professionals—one in pharmaceutical technical and regulatory affairs, and one in health and medicine policy analysis. To reduce the potential bias in the process while ensuring transparency and avoiding potential conflict of interest, the assessment should be carried out by a non-governmental organization (e.g., an academic institution such as university or a private organization). It can also be performed by an international organization.

   It is essential that the assessment, including the appointment of the team and its role and scope of work, is approved by the relevant authority. In many instances, the Ministry of Health or MRA is the responsible body to approve it. This approval should be secured before any activities of the actual assessment begin.

2. Secure a financial budget based on the scope of work and time frame described in the assessment.

3. Communicate information about the assessment to all agencies, responsible authorities, and interested persons to enlist their support and cooperation. These usually include different units or divisions of the MRA (e.g., drug registration, inspection, licensing, laboratory testing, and postmarketing surveillance) and key players in pharmaceutical services (e.g., procurement agents, importers, wholesalers or distributors, manufacturers, and medicines regulators).

DATA COLLECTION METHODS AND TECHNIQUES

A predefined indicatory questionnaire may be used to guide reviewers through collection of the data and the information required for the review and assessment (see Form 12.1). Data collection may be carried out using a combination of techniques:

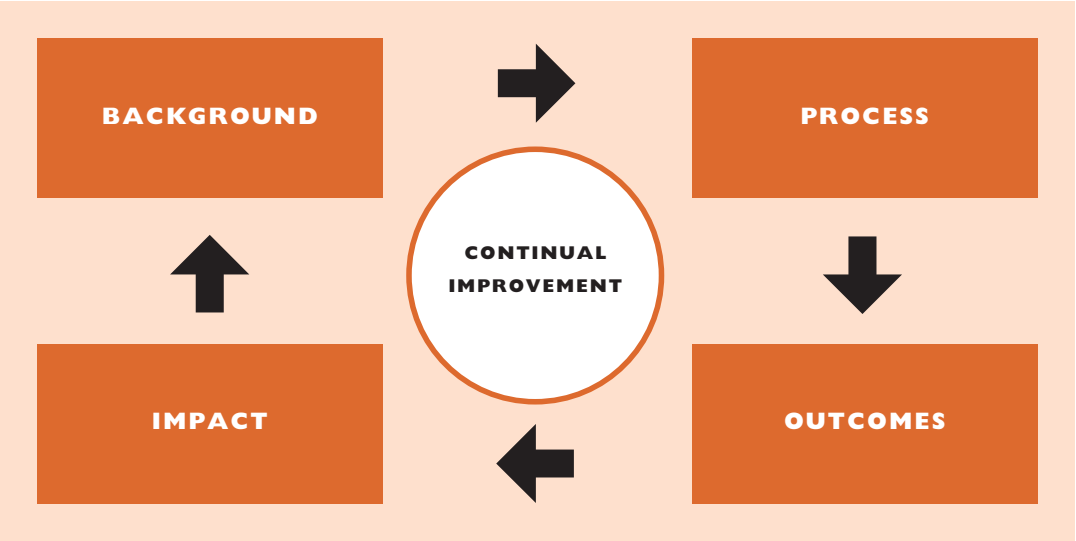

Figure 12.2
Data analysis methodology

- Conducting formal or semiformal discussions and consultations with key officials, to include directors or deputies of chief divisions within the MRA, government, and other procurement agencies, selected key nongovernmental organizations, drug testing laboratories, and selected key pharmaceutical establishments
- Studying and reviewing relevant and accessible (both published and unpublished) technical documents and records from primary and secondary sources. These include medicines laws, executive orders, inspection records, MRA and national laboratory annual or midterm reports, and economic, health and medicine-related indicators
- Using other convenient techniques, such as email, fax, and telephone.

METHODS FOR DATA ANALYSIS

Quantitative data collected for each question in the questionnaire or obtained from other techniques may be examined, analyzed, and computed into percentages (if appropriate) by experts in the field. Where necessary and appropriate, these data can be tabulated and presented in graphs for better presentation purposes.

Relationships between certain constructs of data may be identified to find possible explanations for evaluation of a medicines regulatory system technical and managerial capability and, possibly, system performance.

Each relevant data set or construct representing each aspect of the country's medicine quality assurance and control framework—including premarketing quality assessment, regulatory functions performance, technical components, and postmarketing surveillance—may be analyzed and used to explain "how" and "why" each aspect works or does not work.

The analysis may be based on the principles shown in Figure 12.2 and as presented in the following structure:

Background. General background information on demographic, economic, health, and pharmaceutical context (with key indicators on health and pharmaceutical services of both public and private sectors, medicine regulatory system, medicines quality assurance and control) of the country being reviewed. More specifically, data and information on medicines regulatory functions and responsibilities will be added.

Process. The mechanisms and activities by which an MRA performs. Process indicators are used to assess the effectiveness of these mechanisms and activities, particularly, legislation, regulation and enforcement of drug laws (if any), selection and registration of essential medicines, and human and financial resource allocation for various medicine regulatory activities (e.g., product quality assessment, registration, inspection, testing, and continuing education).

Outcomes. The achievement of common objectives of each country's MRA to address poor-quality medicines in general and, in some cases, focus the assessment on particular disease programs (e.g., medicines to treat malarial or tuberculosis). Outcome indicators would be used to demonstrate the degree to which these objectives are being met.

Impact. The overall impact of the QA/QC activities on the national priority disease programs (e.g., reduction of poor-quality medicines over time and an increased budget allocation by the government for QA/QC work).

Continual improvement. The overall goal for the government (including Ministry of Health, medicines regulatory authority, disease control programs, the national laboratory for medicines quality control) and others to achieve.

It is reasonable to assume that if good results are achieved from process indicators, the outcome indicators should also show positive results or improvement over time. If the outcome indicators suggest significant problems when the structural and process indictors indicate good results, however, policymakers and regulators should investigate the problems, identify causal factors, and revise strategies accordingly.

REPORTING AND RECOMMENDATIONS

The report of the assessment should be based on the findings of data analysis as described in the previous section and should be presented in an appropriate format for easy comprehension and quick action. Main findings and appropriate actions recommended should be included in the report, as should key issues and problematic areas of the QA/QC systems to be addressed. In the recommendations, prioritization of issues and problems to be addressed or areas of strengthening due to the lack of resources or budgetary constraints is critical. Where appropriate, a proposed step-wise process should be described.

Form 12.1
Information collection questionnaire

This questionnaire serves as a guide to obtaining general information and specific data for the review and assessment of a medicines quality assurance program and medicines quality control system. It is organized into four major categories based on the methodological framework described above.

Every effort has to be made to obtain the most up-to-date data and information. If multi-year data are involved, indicate the year next to the data. The names of interviewees or informants should be kept anonymous. The questionnaire consists of three parts:

1. Background information (e.g., country information and demographic, socioeconomic, health, and pharmaceutical data)
2. Premarketing quality assessment
3. Regulatory functions.

BACKGROUND INFORMATION (INDICATE THE YEAR THE DATA WERE COLLECTED)

1. Country information

   a. Area (in square kilometers)

   b. Administrative divisions (number of provinces, states, districts)

2. Demographic and socioeconomic data

   a. Total population

   b. Population distribution (urban vs. rural)

   c. Life expectancy (male/female)

   d. Literacy rate

   e. Gross domestic product per capita (year:)

3. Health and health system data

   a. Infant mortality rate (per 1000 live births)

   b. Maternal mortality rate (per 100,000)

   c. Total government health expenditure

   d. Total value of international aid for health sector

   e. Total number of health facilities both public and private (provide data in the table below). Indicate the year the data were applied:

Health Facilities	Government/Public	Private
Central		
Provincial/State		
District		
Health Center		

4. Pharmaceutical sector data. Indicate the year for which the data apply:

a. Total government pharmaceutical expenditure	
b. Per capita expenditure on medicines	
c. Total value of domestic pharmaceutical production	
d. Total value of imports of finished pharmaceutical products	
e. Total value of imports of APIs	
f. Total value of exports of finished pharmaceutical products	
g. Total value of exports of APIs	

5. Country health and pharmaceutical human resources

Description	Year
Type and number of health professional training schools	
Medical	
Pharmacy	
Others (e.g., dentistry, nursing)	
Number of health professionals	
Total number of medical doctors	
Total number of pharmacists	

6. Country pharmaceutical sector status (specify year)

No. of establishments	Government	Private	Others	Year
Pharmaceutical manufacturing plants				
For APIs				
For finished dosage forms				
For packaging finished dosage forms				
Research-based pharmaceutical industry				
Generic (incl. branded) pharmaceutical product manufacturers				
Pharmaceutical importers				
Pharmaceutical wholesalers				

7. Evolution of drug regulation

a. The year when the drug law or regulation was first introduced

b. The title of the first law/act/regulation enacted

c. Which of the following aspects of drug quality, safety, efficacy are covered by present drug law(s) or regulations?

Registration	☐ Yes	☐ No
Drug product licensing	☐ Yes	☐ No
Pharmaceutical establishment licensing	☐ Yes	☐ No
Control of pharmaceutical importation	☐ Yes	☐ No
Control of pharmaceutical exportation	☐ Yes	☐ No
Inspection services	☐ Yes	☐ No
Monitoring for quality and ADR	☐ Yes	☐ No
Control of pharmaceutical promotion and advertising	☐ Yes	☐ No
Pharmaceutical quality testing/control	☐ Yes	☐ No
Control of clinical trials	☐ Yes	☐ No
Others (specify)		

d. Existence of national medicines policy: ☐ Yes ☐ No

If yes, indicate the year of its promulgation or introduction:

What are the main components of the policy?

e. Existence of national regulatory agency: ☐ Yes ☐ No

If yes, describe its key functions:

□

□

□

□

□

□

□

8. Government budget allocations for medicines regulatory affairs/activities: Has the government budget increased over the last three years?

☐ Yes ☐ No

If yes, provide figures in the following table.

Year	Government budget (in US$)
Current year	
Last year	
The year before	
Etc.	

If no, provide reasons (e.g., introduction of cost-recovery scheme, etc.):

PREMARKETING QUALITY ASSESSMENT AND REGISTRATION

1. Existence of medicinal drug product assessment unit/team for registration

☐ Yes ☐ No

2. Number of officers/professionals responsible for routine drug registration:

And their professional qualifications:

3. Is there a specific budget for medicines registration? ☐ Yes ☐ No

If yes, please specify sources:
Government (year:)

Fees (year:)

4. How many licenses have been issued, renewed, suspended, or revoked in the last three years?

Action	Year	Year	Year
New licenses issued			
Renewed			
Suspended			
Revoked			
Other (specify)			

5. Are there unlicensed or illegal establishments engaged in the manufacture, import, export, or retail sale of pharmaceutical products in the country? ☐ Yes ☐ No

If yes to any of the above, provide estimated number in the table below.

Type of establishment engaged in	Year	Year
Manufacture		
Import/export		
Wholesale		
Retail sale		

6. Does the country allow the import of unregistered pharmaceutical products?

☐ Yes ☐ No

If yes, please briefly explain under what circumstances (e.g., donated medicines or emergency):

7. What key professional qualifications are required to obtain a license to engage in or operate the following pharmaceutical activities?

Practice/activity	Professional requirement
Manufacturing	
Importing/exporting	
Wholesaling	
Retail selling/pharmacy	

8. Is GMP compliance and inspection of the manufacturing site a precondition for registration of a manufacturing plant?

☐ Yes ☐ No

9. Key technical requirements for medicines registration:

a. Product quality, safety, and efficacy data	☐ Yes	☐ No
b. Interchangeability data (e.g., bioequivalence) for generic	☐ Yes	☐ No
c. Clinical trials data	☐ Yes	☐ No
d. Registration in other countries	☐ Yes	☐ No

10. Are the same requirements applied to both innovator (branded) products as well as generics?

☐ Yes ☐ No

If no, what requirements are different:

11. Pharmaceutical product assessment (for registration) capability:

Maximum number of pharmaceutical products assessed per year

Number of actual pharmaceutical products assessed in

i. Year (e.g., 2001)

ii. Year (e.g., 2002)

iii. Year (e.g., 2003)

12. Pharmaceutical product registration:

a. Number of pharmaceutical products/preparations officially registered in the country (Year) of which

Generic (including branded generic)

13. Registration validation is for:

a. ☐ 2 years

b. ☐ 3 years

c. ☐ 4 years

d. ☐ 5 years

e. ☐ > 5 years

14. Average fees/costs for a medicine registration: (US$)

15. Lead time (i.e., the time span between application submission and the date of issuance of the license) taken for registering a pharmaceutical product:

16. Existence of fast-track registration system: ☐ Yes ☐ No

If yes, indicate conditions for a product to be eligible for fast-track registration:

17. Are guidelines or instructions on medicine registration available and freely accessible?

a. ☐ On the Internet or World Wide Web

b. ☐ In paper copies

18. Current registration system:

a. ☐ Manual

b. ☐ Computer-assisted

REGULATORY FUNCTIONS

(Central administration: Allows the functioning of regulatory authority, quality control, inspection services, control of pharmaceutical promotion, advertising, and recall).

A. Central administration

1. Existence of a central administration office that oversees key pharmaceutical activities and functions (product assessment, licensing of persons, premises, and practices, registration, inspection, and post-marketing surveillance):

☐ Yes ☐ No

If yes, name it:

2. Professional qualification and the number of people working at central administration; provide year when data/information is obtained.

Qualification	Pharmacy/Pharmaceutical Sciences	Medical Sciences	Other
Postgraduates			
Graduates			
Technicians			
Other (specify)			

3. Professional qualifications and the number of people working in the following functions; provide year when data/information is obtained.

Function	Postgraduates	Graduates	Other (specify)
Drug product assessment			
Licensing			
Registration			
Inspection			
Postmarketing			
Other (specify)			

B. Laboratory control and testing

1. Existence of a national medicine quality control laboratory (NMQCL)

☐ Yes ☐ No

If yes, obtain the following data and information:

2. Number and name of each unit or division of the lab:

Number of units/divisions:

Name of each unit/division:

3. Professional qualification and the number of people working at NMQCL; provide year when data/information is obtained.

Qualification	Pharmacy/Pharmaceutical Sciences	Chemistry	Other
Postgraduates			
Graduates			
Technicians			
Other (specify)			

4. What kind of tests or assays can the lab perform?

a. Identification	☐ Yes	☐ No
b. Hardness (for solid form)	☐ Yes	☐ No
c. Loss on drying	☐ Yes	☐ No
d. Melting range	☐ Yes	☐ No
e. Residue on ignition	☐ Yes	☐ No
f. Disintegration	☐ Yes	☐ No
g. Dissolution	☐ Yes	☐ No
h. Assay for content of API(s)	☐ Yes	☐ No
i. Any of the following special tests?		
☐ Sterility	☐ Yes	☐ No
☐ Pyrogen	☐ Yes	☐ No
☐ Bacterial endotoxin	☐ Yes	☐ No
☐ Bioavailability	☐ Yes	☐ No
☐ Bioequivalence	☐ Yes	☐ No
☐ Other (specify)		

5. The lab is capable of conducting the test for:

a. Impurities (ordinary impurities)	☐ Yes	☐ No
b. Water content	☐ Yes	☐ No
c. Heavy metals	☐ Yes	☐ No

6. Existence of a national pharmacopeia:

☐ Yes ☐ No

If yes, provide name, year first published, and current edition:

7. Name of pharmacopeias officially accepted for use in the country:

□

□

□

□

□

□

8. Functioning laboratory equipment and instruments: Specify in the table below all equipment and instruments the lab possesses and provide the information required.

Description of Equipment/ Instrument	Model/Type	Quantity Introduced	Year	Functioning Status
[e.g., dissolution tester]	[Pharma Test PTZ1E]	[1]	[1996]	[Working; requires calibrating]

9. Estimated maximum number of samples (including APIs and finished products) the lab is able to test per year:

10. Tests (with results) that were performed by the lab in the current and last three years:

Total No. Samples Tested	No. Passed Quality Testing	No. Failed Quality Testing
APIs		
Year:		
Year:		
Year:		
Year:		
Finished pharmaceutical products		
Year:		
Year:		
Year:		
Year:		

11. Specify the most common medicine groups (e.g., antibiotic, antipyretic, anti-inflammatory, etc.) the lab has tested:

□

□

□

12. Sites that have sent medicine samples or APIs and requests for tests:

(e.g., inspection unit of Department of Food and Drugs)

□

□

□

13. Purposes for quality testing of medicine samples in the last two years:

Purpose	No. and Year	No. and Year
Registration		
Quality monitoring		
Manufacturing (in process control)		
Request from drug industry		
Request from individuals		
Administrative or regulatory action		
Other (specify)		

14. Does the lab charge fees for testing services? ☐ Yes ☐ No

If yes, indicate the average charge per sample testing:
US$

15. Total annual budget for the lab operation including salaries of staff

US$ (year)

16. Total annual budget for the lab equipment/instrument maintenance

US$ (year)

17. Major sources of budget for the lab operations/activities, specify:

18. Has the lab received any technical, financial, or in-kind support from any international agencies since its establishment?

If yes, indicate estimated value or type of equipment and year of support:

year

year

year

year

year

19. Main constraints faced in conducting the various tests/assays in the lab:

Circle all answers that apply:

a. Financial constraints—low government budget
b. Limited numbers of qualified professionals
c. Lack of continuing education/training
d. Limited number of adequate lab equipment/instrument
e. Unavailability of certain reference standards/substances
f. Unavailability of pharmacopeial specifications
g. Unavailability of certain reagents, solvents, and indicators
h. Other (specify)

20. Lab management with regard to good laboratory practices

Circle all answers that apply:

a. Existence and use of sample receiving/collection notebook
b. Existence and use of laboratory notebook
c. Existence and use of analytical work book or work sheet
d. Existence and use of lab equipment log book

e. Existence (in written document) of safety rules and measures applied
f. Existence and use of appropriate lab clothes, gloves, goggles, etc.
g. Existence and use of appropriate and separate storage room for reference substances, toxic and poisonous materials, and inflammable chemicals.
h. Working reagents, references, solutions, solvents, and samples are appropriately labeled (at least their name, concentration, date of preparation, initial of preparer, count, as necessary)
i. Existence and use of standard operating procedures for testing
j. Existence and use of air-sucking chamber
k. Other

21. Has the lab participated in any international or regional assessment for professional and technical competency? ☐ Yes ☐ No

If yes, describe the event and the year:

22. Has the lab ever been requested to test a certain product's quality by an international agency or neighboring countries? ☐ Yes ☐ No

If yes, describe the event and the year:

23. Has the lab received any complaints regarding its testing results in the past three years? ☐ Yes ☐ No

If yes, describe the event and the year:

C. Inspection services

1. Existence of provisions in the medicines law/regulations defining the powers and status of GMP inspectors: ☐ Yes ☐ No

2. Existence of a GMP inspectorate: ☐ Yes ☐ No

If yes, provide number of inspectors and indicate whether they also serve as inspectors for medicines supply chain:

If no, indicate whether inspection services are subcontracted:

3. Relationship of GMP inspectorate to the unit/division in charge of licensing of manufacturers and product registration unit/division:

4. Existence of national GMP guidelines: ☐ Yes ☐ No

If yes, give its name and year of introduction:

(year)

If no, what GMP guidelines are officially accepted for use in the country?

5. Existence of manuals or standard operating procedures (SOPs) for GMP inspectors:
☐ Yes ☐ No

If yes, provide name and date of publication:

(year)

6. Status of application of GMP guidelines/standards for manufacturing plants:

Voluntary Compulsory (required by law)

7. Information on current GMP inspection-related activities:

No. of Plants and Type of Inspection	**Year**	**Year**	**Year**
Total no. of manufacturing plants in the country			
No. of plants inspected and compliant to GMP			
No. of plants inspected for renewal of license			
No. of plants inspected because of complaints			
No. of plants inspected as follow-up			
Other (specify)			

8. Number of administrative or regulatory measures taken against GMP noncompliant manufacturing plants in the last three years:

Measures Taken	Year	Year	Year
Written notice of warning			
Fines			
License suspended			
License revoked			
Production suspended			
Other (specify)			

9. Plan to increase number of manufacturing plants to comply with GMP standards:
☐ Yes ☐ No

If yes, indicate target number by year:

Target to Increase GMP Compliance	Current Year	Year	Year
No. of GMP noncompliant manufacturing plants			
No. of GMP compliant plants			

10. Inspections in the medicines supply/distribution chain—existence of inspection services in the medicines supply chain: ☐ Yes ☐ No

If yes, indicate number of inspections per year planned:

11. Are samples collected during inspections? ☐ Yes ☐ No

If yes, provide information below:

Samples Collected and Tested in Connection With:	No. of Samples Collected / Year	Passed Quality Testing / Year	Failed Quality Testing / Year
GMP inspection	/	/	/
Supply chain inspection	/	/	/
Other (specify)	/	/	/
Total	/	/	/

12. Number of administrative or regulatory measures taken against practices related to producing or selling poor-quality products in the last 3 years:

Measures Taken	Year	Year	Year
Written notice of warning to manufacturer, wholesaler, and retailer			
Fines			
License suspended			

Measures Taken	Year	Year	Year
License revoked			
Product recall			
Product withdrawal			
Other (specify)			

13. Does the inspectorate charge fees for inspection services? ☐ Yes ☐ No

If yes, indicate rough fees charge per inspection: US$

14. Existence of mechanism or system for monitoring of quality of medicines as postmarketing surveillance activity: ☐ Yes ☐ No

If yes, briefly describe the mechanism

15. Existence of product quality and adverse medicine reactions reporting mechanism or system: ☐ Yes ☐ No

If yes, briefly describe the mechanism:

16. Existence of product recall mechanism or system: ☐ Yes ☐ No

If yes, briefly describe the mechanism:

17. Main constraints faced in carrying out inspection services.

Circle all answers that apply:

a. Financial constraints—low government budget
b. Limited numbers of qualified inspectors
c. Lack of continuing education/training
d. Lack of SOP or guidelines
e. Limited access to relevant information on inspection
f. Other (specify)

D. Licensing of persons, pharmaceutical establishments, or both

1. Existence of unit/team in charge of issuing, variation, suspension, and revocation of license for persons or pharmaceutical establishments: ☐ Yes ☐ No

2. Number of officers/professionals responsible for routine licensing:

Their professional qualifications:

3. Existence of standard operating procedures (SOPs) for licensing of persons or pharmaceutical establishments: ☐ Yes ☐ No

If yes, provide name and date of publication:

4. What are the main requirements and qualifications to be met for license approval of a retail pharmacy?

☐ Specified location
☐ Specified list of medicines
☐ Other(s)
☐ Professional qualification (e.g., pharmacist)
☐ Completion of pharmacy training program

5. What are the main requirements and qualifications to be met for license approval of a pharmaceutical wholesaler or distributor?

☐ Specified location
☐ Professional qualification (e.g., pharmacist as technical manager)
☐ Adequate facility with proper air ventilation and air conditioning
☐ Appropriate storage areas (cold, cool, and room temperature rooms)
☐ At least 80% of the transport means are in good working conditions
☐ Other(s)

6. How many licenses have been issued, renewed, suspended, or revoked in the last 3 years?

Action	**Year**	**Year**	**Year**
New licenses issued			
Renewed			
Suspended			
Revoked			
Other (specify)			

7. Are there unlicensed or illegal establishments engaged in the manufacture, import, export, or retail sale of pharmaceutical products in the country? ☐ Yes ☐ No

If yes to any of the above, provide estimated number in the table below.

Type of Establishment Engaged in	Year	Year
Manufacture		
Import/export		
Wholesale		
Retail sale		

E. Other relevant questions—pose to key stakeholders (e.g., pharmacies, distributors/importers/wholesalers, and manufacturers) during the visit to their premises. The data collection team should be accompanied by the relevant authority (e.g., drug regulatory agency personnel) to visit the premises.

1. Retail medicines outlets or pharmacies

Is the premise operating under a valid license (i.e., has it been licensed by the relevant medicines authority and is the license still valid)?
☐ Yes ☐ No

Is the outlet attendant the person who holds the license?
☐ Yes ☐ No

What are main sources of the medicines sold in the outlet?
Check all that apply:

☐ Direct from local manufacturing companies
☐ From main domestic wholesaler(s)
☐ Other sources

Has the outlet kept all documents or papers, such as invoices, that can be used to trace the sources of medicines purchased?
☐ Yes ☐ No

Any expired-date products found on the premise?
☐ Yes ☐ No

Does the outlet have a refrigerator to store medicines requiring cold temperature?
☐ Yes ☐ No

Have medicines been kept out of direct sunlight?
☐ Yes ☐ No

Has the premise been inspected by the inspector(s) from MRA?
☐ Yes ☐ No

If yes, provide the number of occasions inspected by year:

Number of Inspections	Purpose of Inspection	Year

2. Wholesaler/distributor

a. Is the company operating under a valid license (i.e., has it been licensed by the relevant drug authority and is the license still valid)?
☐ Yes ☐ No

b. What are the main sources or suppliers of the medicines sold by the wholesaler?
Check all that apply:
☐ Direct from local manufacturing companies
☐ Direct from foreign manufacturers
☐ From foreign or international distributors/suppliers
☐ Other sources

c. Have the sources or suppliers of medicines prequalified?
☐ Yes ☐ No
If yes, by whom?
☐ National MRA
☐ International agency, please name it:

d. Was preshipment or postshipment inspection carried out by the company before accepting any consignment? ☐ Yes ☐ No

If yes, by whom?
☐ QA/QC personnel of the company
☐ National MRA official
☐ Subcontracting private entity

e. Has the company kept all documents or papers, such as invoices, that can be used to trace the sources of medicines purchased?
☐ Yes ☐ No

f. Does the premise storage facility have cold and cool rooms?
☐ Yes ☐ No

g. Does the storage facility have the following critical components?
Check all that apply:
☐ Incoming medicines receiving area
☐ Quarantine area or room
☐ (Basic) laboratory testing facilities or room
☐ SOPs for receiving and storing medicines
☐ Inventory control system (manual/ computerized)

h. Any expired-date products found in the premise?
☐ Yes ☐ No

i. Does the premise have appropriate air ventilation and air conditioning?
☐ Yes ☐ No

j. Has your premise been inspected by the inspector(s) from MRA?
☐ Yes ☐ No
If yes, provide the number of occasions inspected by year:

Number of Inspections	Purpose of Inspection	Year

k. What is your opinion of the current system of medicines registration in terms of process (transparency, effectiveness), application time, availability of clear instructions, and fees:

CHAPTER 13

Bioavailability and Bioequivalence: When Documents or Data Are Required

This chapter provides recommendations to medicines regulatory authorities (MRAs) and other relevant agencies on the requirements of a generic (multisource) pharmaceutical product approval for registration or procurement purposes.

All pharmaceutical products, including generic products, should be used only after approval by local authorities. To authorize the marketing of a generic pharmaceutical product, MRAs are advised to require documentation indicating that the product meets the established (1) good manufacturing practices (GMP); (2) quality controls; (3) product characteristics, including labeling; and (4) pharmaceutical product interchangeability for quality, safety, and efficacy with the comparator product (see the further discussion on choices of comparator products in this section). With some classes of product, including parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of GMP and evidence of conformity with relevant pharmacopeial specifications (World Health Organization, 1999d).

Assessment of equivalence normally requires an *in vivo* study or a justification that such a study is not required (i.e., a biowaiver[19] based on the Biopharmaceutics Classification System [BCS]) (United States and Food and Drug Administration, 2003a). Bioequivalence studies include pharmacokinetic studies, pharmacodynamic studies, and comparative clinical trials. In selected cases, *in vitro* dissolution profile comparison of the multisource product with the comparator product or dissolution studies may be sufficient to provide indication of equivalence.

Definitions

Bioavailability (BA). Bioavailability is the rate and extent of availability of an active ingredient from a dosage form as measured by its concentration/time curve in the systemic circulation or its excretion in the urine.

Bioequivalence (BE). Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent, and their bioavailability, after administration in the same molar dose, is similar to such a degree that their effects can be expected to be essentially the same.

Assessment of Documents for Equivalence

MRAs or procurement agencies may use pharmacokinetic measurements and *in vitro* methods to conduct an assessment of bioequivalence studies for most orally administered pharmaceutical products for systemic exposure.

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by an MRA depends on many factors, including characteristics of the active pharmaceutical ingredient (API) and the finished medicine product. When a medicine produces meaningful concentrations in an accessible biological fluid such as plasma, comparative pharmacokinetic studies can be acceptable. When appropriate, *in vitro* testing and BCS-based biowaivers for immediate-release drug products (i.e., those that are highly soluble, highly permeable), and for those that rapidly dissolve (i.e., 85 percent or greater in 15 minutes or less in pH 1.2, 4.5, and 6.8) (United States Food and Drug Administration, 2001) can assure equivalence between the multisource product and the comparator product (Lindenberg et al., 2004). When a drug does not produce measurable concentrations in an accessible biological fluid, comparative pharmacodynamic studies are a further alternative to document equivalence (Yu et al., 2002; Kasim et al., 2004). Comparative clinical trials are generally most insensitive to documenting equivalence or interchangeability, but when it is not possible to determine the pharmacokinetic profile or to find suitable pharmacodynamic endpoints, comparative clinical trials can be considered appropriate.

When Equivalence Studies Are Not Necessary

The following types of pharmaceutical products are considered to be equivalent without the need for further documentation requirements, and BE testing is also not required (Yu et al., 2002):

- When the product is to be administered as an aqueous intravenous solution containing the same API in the same molar concentration as the comparator product (similarly for those administered by other parenteral routes—e.g., intramuscular, subcutaneous—as aqueous solutions)
- When the products are solutions for oral use (including syrups, elixirs, tinctures, or other soluble forms, but not suspensions) containing the API of the same molar concentration as the comparator product, and contain only excipients known to have no effect on gas-

trointestinal (GI) transit, GI permeability, and hence, absorption or stability of the API in the GI tract

- When pharmaceutically equivalent products are powders for reconstitution as a solution and the solution meets either criterion above
- When pharmaceutically equivalent products are gases
- When pharmaceutically equivalent products are optic or ophthalmic or topical products prepared as aqueous solutions and contain the same APIs in the same molar concentration and essentially the same excipients in comparable concentrations
- When pharmaceutically equivalent products are solutions for aerosol or nebulizer inhalation products or nasal sprays, tested to be administered with or without essentially the same device, prepared as aqueous solutions, and contain the same APIs in the same concentration and essentially the same excipients in comparable concentrations.

When Equivalence Studies Are Necessary

Documentation of equivalence should be requested by an MRA's registration or procurement agency for a generic pharmaceutical product in which the product is compared to the reference or comparator product. Studies should be carried out based on the formulation intended for marketing.

In vivo studies

In vivo documentation of equivalence is needed when there is a risk that possible differences in bioavailability may result in therapeutic nonequivalence (United States Food and Drug Administration, 2003b). Some examples are listed below.

- Oral immediate-release pharmaceutical products with systemic action when one or more of the following criteria apply:
  - Narrow therapeutic range (efficacy/safety margins);
  - Documented evidence for bioavailability problems; or
  - Excipients and pharmaceutical processes used in manufacturing known to affect the bioequivalence.
- Non-oral and nonparenteral pharmaceutical products designed to act by systemic absorption (such as transdermal patches, suppositories, testosterone gel, and skin-inserted contraceptives).
- Modified-release pharmaceutical products designed to act by systemic absorption (United States Food and Drug Administration, 2003b).[20]
- Fixed-dose combination products with systemic action, in which at least one of the active pharmaceutical ingredients requires an *in vivo* study.

For the products listed above, plasma concentration measurements over time are sufficient proof for equivalence. Alternatively, comparative pharmacodynamic or clinical studies can be used.

In vitro studies

For certain drugs and dosage forms, documentation of equivalence may be assessed by the use of *in vitro* dissolution testing. Some examples follow:

- Drug products for which *in vivo* studies are not required.
- Immediate-release tablets with different strengths of a generic formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, when:
  - All strengths are proportionally similar in formulation;
  - An appropriate equivalence study has been performed on at least one of the strengths of the formulation; and
  - The dissolution profiles among the strengths are similar.
- Extended-release capsules or tablets, when the drug product is in the same dosage form but in a different strength, and is proportionally similar in its active and inactive ingredients and has the same drug release mechanism.
- Biowaivers based on Biopharmaceutics Classification System.

Generic products used in BE studies

Generic products used in BE studies for registration purposes should be identical to the projected commercial pharmaceutical product. Therefore, not only the composition of the dosage formulation and other characteristics, including labeling, but also the manufacturing process, should be the same as those to be used in future routine production. Test products must be manufactured under GMP requirements. Batch control results of the test or sample product, the lot or batch numbers of both test and comparator products, and the expiration date for the comparator product should be stated.

Ideally, samples to be used in BA or BE studies should be taken from industrial-scale batches.

Potency and *in vitro* dissolution characteristics of the generic and the comparator pharmaceutical products should be ascertained before a BE study is performed. The content of APIs of the comparator product should reflect the label claim, meeting the pharmacopeial acceptance specifications or that of validated procedures.

Choice of comparator product

In the course of evaluating the documentation on bioequivalence, verify what comparator product was used for a generic pharmaceutical product. Ideally, an innovator product whose quality, safety, and efficacy have been well assessed and documented in premarketing studies and postmarketing surveillance schemes should be used as a comparator.

However, for many pharmaceutical products, an innovator product cannot be identified; in some cases an innovator product no longer exists or is not available on the market. The selection of the comparator product is usually made at the national level by the medicines regulatory authority. The possible options are, in order of priority:

- To select the innovator product, if in existence, that has been established for quality, safety, and efficacy
- To choose the national market leader, if in existence, for which pharmaceutical quality, safety, and efficacy have been established
- If none of the above is possible, the MRA is encouraged to consider a product available on another market, which has been established for quality, safety, and efficacy by an other national MRA.

The U.S. Food and Drug Administration has created a list of approved drug products with therapeutic equivalence that can be used for equivalence evaluations (United States Food and Drug Administration, 2004). The World Health Organization has also initiated a list of comparator products for equivalence assessment of interchangeable multisource products, which provides recommendations for choosing comparator product in cases where the innovator product is not available (World Health Organization, 2002a, pp. 161–180). In either circumstance, the applicant should justify the choice of comparator product used for the study.

Evaluation of BA/BE documents

In addition to the above requirements, MRAs or the quality assurance officer should carefully evaluate the study design and methodology, including the following:

- Selection of dose: The highest marketed strength should be used for the equivalence study. A higher dose may be employed when analytical difficulties exist. In certain cases, a study performed with a lower strength can be considered acceptable, if a lower strength is chosen for reasons of safety.
- Sampling times of blood samples should be taken at a frequency sufficient for assessing Cmax (maximum concentration), AUC (area under curve) and other parameters. Sampling points should include a predose sample, 1–2 points before Cmax, 2 points around Cmax, and 3–4 points during the elimination phase. In total, about 7 points should be taken for estimation of the required pharmacokinetic parameters.
- Parameters to be assessed: Area under the plasma or serum or blood concentration-time curve from time zero to time t (AUC0-t). Cmax is the observed maximum or peak concentration representing peak exposure of drug (or metabolite) in plasma, serum or whole blood. AUC0-t and Cmax are considered to be the most relevant parameters for assessment of bioequivalence.
- Acceptance range: 90% confidence interval of the test to the comparator or reference ratio of AUC falls within 80%–125% and a general acceptance limit 0.80–1.25 should be applied for Cmax ratio (Palylyk-Colwell et al., 1998; World Health Organization, 1999e).
- Reporting of results: The report of a bioequivalence study should give the complete documentation of its protocol, conduct, and evaluation complying with good clinical practice. Many have used the International Conference on Harmonization guidelines in the preparation of their study report. The responsible investigator should sign their respective sections of the report. Names and affiliations of the responsible investigators, site of the study, and period of its execution should be stated. The names and batch numbers of the pharmaceutical products used in the study, as well as the composition of the tests prod-

ucts, should be given. Results of *in vitro* dissolution tests should be provided. In addition, the applicant should submit a signed statement confirming the identity of the test product with the pharmaceutical product that is submitted for registration (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1995).

For fixed-dosed combination pharmaceutical products

The problem of bioavailability is more apparent if a fixed-dose combination medicine that is usually purchased from one manufacturer is replaced with the same product, in the same dosage form, and in the same amount, from a different manufacturer. Even though the two products may contain the correct amount of active ingredients, the new preparation may not give the expected therapeutic result. In such a situation, a comparative bioavailability study is particularly important. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent, and their bioavailability, after administration in the same dose, is similar to such a degree that their effects can be expected to be essentially the same.

In order to confirm that pharmaceutical product being registered, procured, or used can produce the expected therapeutic result, the MRA and procurement agencies must request that suppliers submit bioavailability or bioequivalence (for multisource or generic pharmaceutical products) data as follows (Phanouvong et al., 2002):

- Bioavailability, bioequivalence (or both) study details, including study design, procedures, calculation methods, results, and assessment for all components of fixed-dose combinations;
- Dissolution profile of the same batch used for bioavailability/bioequivalence study of all components; and
- Dissolution data for the specific batches shipped (requested with each delivery of fixed-dose combination).

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[19] Examples are acetysalicylic acid, Chloroquine (phosphate/sulfate), quinine, pyrazinamide, Salbutamol (sulfate), Stavudine (d4T), and Zidovudine (ZDV or AZT).

[20] In some instances, product marketing authorization may be based on *in vitro–in vivo* correlation information and *in vitro* data of modified-release drug products provided it is not the first (original) approval of the modified-release dosage form.

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GLOSSARY OF TERMS

The terms listed here are defined specifically for use with this guide. Different definitions may appear in other documents, including the appended forms, many of which were published some years ago. Some are adopted from existing sources such as the World Health Organization, Management Sciences for Health, and the United States Pharmacopeia.

In this guide the terms medicine, drug, drug product, and pharmaceutical product are interchangeable.

Abbreviated new drug application (ANDA). A simplified submission process for duplicate drugs or for drugs that have already been approved. ANDAs are used for products with the same or closely related active ingredients, dose forms, strengths, routes of administration, use, and labeling as a product that has already been shown to be safe and effective.

Active pharmaceutical ingredient (API). A substance or compound intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

Adverse drug reaction (ADR). Any unwanted effect produced by a drug that is harmful to the patient. Onset may be sudden or develop over time.

Applicant. An applicant is a company or person who submits an application, an abbreviated application, or an amendment or supplemental application to seek MRA approval for a new drug or for an antibiotic drug. An applicant can also be a person who owns and approved application or abbreviated application.

Assay. The monograph standard test, with associated method of analysis, which is designed to determine the strength of a drug product.

Basic tests. Simplified analytical tests that do not require complex methodologies and equipment. Basic tests may be used to verify the identity of a drug or to ascertain the absence of gross degradations or contamination.

Batch (or lot). A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that the product could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. A batch may need to be divided into smaller batches, which are later combined to form a final homogeneous batch.

Batch certificate. A document containing information (as set out in Form 5.1) that is usually issued for each batch by the manufacturer, or validated or issued by the competent authority of the exporting country, particularly for vaccines, sera, and other biological products. The batch certificate accompanies every major consignment.

Batch (or lot) number. A distinctive combination of numbers, letters, or both that specifically identify a batch on the labels, the batch records, and the certificate of analysis, etc.

Bioavailability (BA). The rate and extent of availability of an active ingredient from a dosage form

as measured by its concentration/time curve in the systemic circulation or its excretion in the urine.

Bioequivalence (BE). Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent, and their bioavailability, after administration in the same molar dose, is similar to such a degree that their effects can be expected to be essentially the same.

Bulk drug substance. Any substance represented for use in a drug, and during manufacturing, processing, or packaging that becomes an active ingredient of a finished dosage form. Bulk drug substances do not include intermediates used in the synthesis of such substances.

Bulk product. Any product that has completed all the processing stages up to, but not including, final packaging.

Central medical stores (CMS). Drug supply mechanism in which drugs are financed, procured, and distributed by the government, which is the owner, funder, and manager of the entire supply system.

Certificate of analysis. Report of the analytical test results obtained, including the final conclusion of the examination of a sample issued by the manufacturer, repackager, or trader.

Clinical trial (or clinical research). A research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are the fastest and safest way to find treatments to improve health. Interventional trials determine whether experimental treatments, or new ways of using known therapies, are safe and effective under controlled environments. Observational trials address health issues in large groups of people or populations in natural settings.

Counterfeit drug. A pharmaceutical product that is deliberately and fraudulently mislabeled with respect to identity or source. Both branded and generic products can be counterfeited. Counterfeit drugs can include products with the correct ingredients, with the wrong ingredients, without active ingredients, with insufficient quantity of active ingredients, or with fake packaging. A counterfeit drug can be a deliberate imitation or a copy of a genuine product.

Disintegration. The breaking up of a tablet or a capsule into granules or aggregates in an aqueous fluid.

Dispenser. A dispenser is any person authorized by national regulations to issue or dispense medicines. Dispensers include pharmacists, pharmacy assistants, pharmacy technicians, nurses, or other health care providers.

Dissolution. The process by which a solid substance is separated into molecules or ions that homogeneously disperse in an aqueous fluid to form a solution. The rate of dissolution is determined by the interaction between the substance and the medium.

Dosage form. The form—tablet, capsule, injection—of a completed pharmaceutical preparation.

Dosage (or strength). The content of the active ingredient per dosage unit is determined by the assay of the specific monograph and expressed, generally, in milligrams or units per dosage unit.

Drug. Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Drug formulation. The composition of a dosage form, including the characteristics of its raw materials and the operations required to process the drug.

Drug interaction. A modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action of either substance or may be an adverse effect that is not normally associated with either drug. The action of one drug upon another may be harmful to the patient, depending on the drugs and the patient's medical condition.

Drug product. A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance generally, but not necessarily, in association with one or more other ingredients.

Drug substance. An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredients.

Efficacy (of a medicine or treatment). The maximum ability of a medicine or treatment to produce a result regardless of dosage. A medicine passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. For example, in the procedure mandated by the United States Food and Drug Administration, Phase II clinical trials gauge efficacy and Phase III trials confirm efficacy.

Essential medicines. Medicines that satisfy the priority health care needs of a population. Essential medicines are selected with due regard for public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in appropriate dosage forms, with assured quality and adequate information, and at a price that individuals and communities can afford.

Expiry (or expiration) date. The date up to which a product is expected to remain within specifications, if stored correctly. Expiry date is established by the manufacturer for each batch by adding the shelf-life period to the date of manufacture.

Finished product. A product that has undergone all stages of production, including packaging, in its final container and labeling.

First-Expired First-Out (FEFO). An inventory management method in which products with the earliest expiry date are the first products issued, regardless of the order in which they are received. This method is more demanding than FIFO (see below) and should be especially used for short-dated products such as vaccines.

First-In First-Out (FIFO). An inventory management method in which the first products received are the first products to be issued. This method generally minimizes the risk of drug expiration.

Fixed-dose combination (FDC). A combination of more than one active pharmaceutical ingredient in one package or single dosage form.

Generic drug. A generic drug is the same as a brand name drug is dosage, safety, strength, how it is taken, quality, performance, and intended use. Before a generic drug is approved, an MRA should require many rigorous tests and procedures to assure the generic drug can be substituted for a brand name drug.

Generic name. The approved or International Nonproprietary Name of a drug given by the World Health Organization.

Generic products. A pharmaceutical product—usually intended to be interchangeable with the innovator product—is usually manufactured without a license from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

Good clinical practices (GCP). International ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

Good dispensing practices (GDP). Ensures that an effective form of the correct drug is delivered to the right patient, in the prescribed dosage and quantity, with clear instructions, and in a package that maintains the potency of the drug.

Good dispensing and storage practices (GDSP). A standard for the preparation, dispensing, and storing of medicines to ensure a preparation's integrity, including its appearance, until it reaches the user.

Good laboratory practices (GLP). Those quality systems concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived, and reported. The principles of good laboratory practices can be the basis for ensuring the quality, reliability, and integrity of studies, the reporting of verifiable conclusions, and the traceability of data.

Good manufacturing practices (GMP). The part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled by the quality standards appropriate to their intended use and as required by the marketing authorization. These standards include criteria for personnel, facilities, equipment, materials, manufacturing operations, labeling, packaging, quality control, and in most cases, stability testing.

Good pharmacy practices (GPP). Recommended national standards for the promotion of health; the supply of medicines, medical devices, and patient

self-care; and the improvement of prescribing and medicine use through pharmacists' activities.

Identity. The correct chemical substance and formula of an active ingredient in a drug product.

Identity test. The selected test in the monograph to verify that the API is correct for that drug product.

Indication. A symptom or circumstance that indicates the advisability or necessity of a specific medical treatment or procedure. Indication could also refer to the degree indicated in a specific instance or at a specific time on a graduated physical instrument, such as a thermometer.

Interchangeable pharmaceutical product. A product that is therapeutically equivalent to a reference product.

International nonproprietary names. International nonproprietary names facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name. Proposals for recommended international nonproprietary names are submitted to the World Health Organization on a form provided by WHO by the purpose. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

Labels (according to GMP). All finished drug products should be identified by labeling, as required by national legislation, bearing at least the following information:

(a) The name of the drug product

(b) A list of the active ingredients (if applicable, with the International Nonproprietary Names), showing the amount of each active ingredient present, and a statement of the net contents (number of dosage units, mass, or volume)

(c) The batch number assigned by the manufacturer

(d) The expiry date and manufacturing date in an uncoded form

(e) Special storage conditions or handling precautions that may be necessary

(f) Directions for use, and any warnings or precautions that may be necessary

(g) The name and address of the manufacturer or the company or person responsible for placing the product on the market.

Lead time. The time interval needed to complete the procurement cycle. This begins at the time when new stock is ordered and ends when that stock is received and available for use. Lead time varies depending on the system, speed of deliveries, availability, and reliability of transport, and sometimes, weather.

Manufacture. All operations involved in the purchase of materials and products, production, quality control, release, storage, shipment of finished products, and related controls.

Manufacturer. A company that carries out at least one step of manufacture.

Manufacturing or processing. Manufacture, preparation, propagation, compounding, or processing of a drug or drugs via chemical, physical, biological, or other procedures that meet the definition of drugs. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further distribution of the drug form the original place of manufacturer to the person who makes final delivery or sale to the ultimate consumer.

Marketing authorization (product license, registration certificate). An official document issued by a competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. The certificate must set out, among other things, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INN or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. The document specifies the information on which authorization is based. The license also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization.

Medicines regulatory authority (MRA). A national body that administers the full spectrum of regula-

tory activities associated with pharmaceuticals, including at least all of the following functions: marketing authorization of new products and variation of existing products; quality controlled laboratory testing (although in some countries, the laboratory may not be part of the MRA); adverse drug reaction monitoring; provision of medicine information and promotion of rational medicine use; good manufacturing practice inspections and licensing of manufacturers, wholesalers, and distribution channels; enforcement of operations; and monitoring of drug utilization.

Method validation. A demonstration of the suitability of the analytical procedure for its intended use. The characteristics of the analytical procedures to be considered in method validation are accuracy, precision, robustness, linearity and range, selectivity, limit of detection, and limit of quantitation.

Ministry of Health. The national governmental agency responsible for providing and monitoring the service and quality of health services provided to its citizens and visitors, including the control of illness and disease in the country.

Monograph. A set of properly selected standardized tests with associated methods of analysis that can be used to assess the integrity of drugs (including dosage forms) and starting materials. These standards, when met, assure the quality of the drug with respect to identity, purity, strength, packaging, storage, and labeling. Monographs are published in pharmacopeia.

Multisource (generic) pharmaceutical. Pharmaceutically equivalent products that may or may not be equivalent therapeutically. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

New drug. A drug that has not been declared safe and effective by qualified experts under the conditions prescribed, recommended, or suggested on the label. This may be a new chemical formula or an established drug prescribed for use in a new way.

Open tender. The formal procedure by which quotations for the supply of drugs, under their generic names, are invited from any local or international manufacturer or representative, subject to the terms and conditions specified in the tender invitation.

Over-the-counter (OTC) medicine. Medicines that can be sold from licensed retail pharmacies or outlets without professional supervision and without a physician's prescription. OTC medicines are considered safe and effective for use by the general public. OTC medicines are suitable for self-medication for minor diseases and symptoms.

Packaging material. Any material, including printed material, used in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Primary packaging materials are those that are in direct contact with the product.

Pharmaceutically equivalent products. Products that contain the same amount of the same active substances in the same dosage form, meet the same or comparable standards, and are intended to be administered by the same route.

Pharmaceutical product. Any medicine intended for human use or administered to food-producing animals, presented in its finished dosage form or as an active ingredient for use in such dosage form, that is subject to control by pharmaceutical legislation in both the exporting and importing states.

Pharmacodynamic. The study of the action or effects of drugs on living organisms.

Pharmacokinetics. The process by which a drug is absorbed, distributed, metabolized, and eliminated by the body.

Pharmacopeia. A book containing an official list of monographs and internationally acceptable standards for the potency, purity, quality, packaging, and labeling of pharmaceutical products. The major pharmacopeias in the world are the International Pharmacopeia, the United States Pharmacopeia, the British Pharmacopoeia, the Japanese Pharmacopeia and the European Pharmacopoeia. Other countries have their own pharmacopeias.

Pharmacovigilance. All science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or other drug-related problems. In general, pharmacovigilance aims to reevaluate the safety and efficacy of pharmaceutical product in the market. This encompasses spontaneous adverse drug reactions, drug information reporting, promotion of rational use of drugs, risk management, and crisis preparedness.

Postmarketing surveillance of medicines quality. Monitoring the quality of drugs by inspection and laboratory testing to assure that the storage is correct and that drugs are stable within their labeled shelf-life.

Potency. The extent to which a drug contains the specified amount of the active ingredient.

Premarketing surveillance. Monitoring the quality of medicines by inspection and laboratory testing to assure that medicines conform to the quality standards and specifications before their marketing authorization.

Primary container. The immediate container in direct contact with the drug product, such as a jar, bottle, blister, ampoule, etc. The primary container is designed to meet the specifications for storage and to protect the drug throughout its shelf-life.

Product certificate. A document containing the information set out in Form 5.1. The certificate is validated and issued for a specific product by the competent authority of the exporting country and intended for use by the competent authority in the importing country, or, in the absence of such an authority, by the drug procurement authority.

Product dossier. The file of a medicine submitted for registration. Such a file should contain details of the product, regulatory situation in other countries, and APIs (with the following characteristics; for example, properties, sites of manufacture, route of synthesis, specification, and stability testing). For finished dosage forms, the file contains formulation; sites of manufacture; manufacturing procedures; specifications for excipients and finished products; container and other packaging; stability testing; labeling; product information; patient information and package inserts; interchangeability; bioequivalence study; and a summary of pharmacology, toxicology, and efficacy of the product.

Product information. Information for health professionals and the public about a product as approved in the exporting country and, when available, a data sheet or a summary of product characteristics approved by the regulatory authority.

Production. All operations involved in the preparation of a pharmaceutical product, from receiving starting materials, through processing and packaging, to completing the finished product.

Product master file. A medicines regulatory authority master file of a drug (submitted by the manufacturer) that contains all information about the efficacy, safety, side effects, purity, strength and quality standards, importer, registration dates, and known drug reactions with other drugs.

Product recall. A process for withdrawing or removing a pharmaceutical product from the distribution chain because of defects in the product or complaints of serious adverse reactions to the product. A recall may be initiated by an MRA, a manufacturer, or by an importer/distributor or a responsible agency.

Provisional marketing authorization. Temporary authorization following initial market inventory, pending full approval by the MRA based on evaluation of quality, safety, and efficacy.

Purity. The extent to which medicines are free from potentially harmful contaminants, degradation products, significant quantities of other drugs, bacteria, or other microorganisms.

Quality (of drug product). All characteristics—purity, strength, packaging, labeling—that allow the drug product to deliver its intended treatment.

Quality assurance (QA). All matters that individually or collectively influence the quality of a product. The objective of QA is to ensure that pharmaceutical starting materials and pharmaceutical products meet quality standards.

Quality control (QC). All measures taken—including setting specifications, sampling, testing, and analytical clearance—to ensure that raw materials, intermediates, packaging materials, and finished pharmaceutical products conform to established specifications for identity, strength, purity, and other characteristics.

Quarantine. Physically isolating the starting, packaging, intermediate, or bulk materials or finished products while a decision is awaited on their release, rejection, or reprocessing.

Recall. The process of withdrawing a medicine from the market because of a quality, safety, or efficacy problem.

Registration. Any statutory system of approval required at the national level as a precondition for introducing a pharmaceutical product to the market.

Safety. Not causing harm or injury, having a low incidence of adverse reactions and significant side effects when adequate instructions for use are given, and having a low potential for harm under conditions of widespread availability.

Sample. A portion of material collected according to a defined sampling procedure. The size of any sample should be sufficient to carry out all anticipated test procedures, including all repetitions.

Sampling procedure. A detailed and complete sampling operation to be applied to a defined material for a specific purpose. A detailed, written description of the sampling procedure is provided as sampling protocol.

Sampling unit. Discrete part of a consignment, such as an individual package, drum, or container.

Secondary container. The external container in which the primary container is placed.

Shelf-life. The period of time during which a drug product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life establishes the expiry date of each batch.

Specification. A detailed document describing the requirements with which the pharmaceutical products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Stability. The ability of a pharmaceutical product to retain its chemical, physical, microbiological, and biopharmaceutical properties within specified limits throughout its shelf-life.

Stability tests. A series of tests designed to obtain information on the stability of a pharmaceutical product to help define its shelf-life and utilization period under specified packaging and storage conditions.

Standard. A technical specification that addresses a business requirement, is implemented in viable commercial products, and to the extent practical, complies with recognized standards organizations such as the International Organization for Standardization (ISO).

Standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material, but of a more general nature (i.e., equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs can be used to supplement product-specific master and batch production documentation.

Starting material. Any substance of defined quality used in the production of a pharmaceutical product, excluding packaging material.

Substandard drug. A legal branded or generic drug that does not meet national or international standards for quality, purity, strength, or packaging.

Therapeutic equivalence. Pharmaceutically equivalent products whose effects with respect to both safety and efficacy are essentially the same, when administered in the same molar dose, as can be derived from appropriate studies (bioequivalence, pharmacodynamic, clinical, or *in vitro*).

Toxicity. An adverse effect produced by a drug that is detrimental to a patient's health. The level of toxicity associated with a drug will vary depending on the condition that the drug is used to treat.

Validated method. A method of analytical performance demonstrated by experimental data that has proven its suitability as analytical support of a specification proposed for particular drug. The nature of the method and the type of drug test determine the characteristics that should be considered to validate the method.

Value-added tax. Government controlled or regulated costs payable upon importation of goods.

WHO-type certificate. A certificate of a pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. (See Forms 5.1, 6.1, and 6.2.)

REQUEST FOR COMMENT ON THE GUIDE

As the final user of this Operational Guide, you can give us valuable advice about its content, lay-out, and usability. Your comments will be carefully considered as we prepare the final edition of the Guide after a year or two of field testing.

Comments

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Thank you!

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