Ensuring the Quality of Medicines in Resource-Limited Countries

AN OPERATIONAL GUIDE




UNITED STATES PHARMACOPEIA
DRUG QUALITY AND INFORMATION PROGRAM

IN COLLABORATION WITH

World Health Organization

National Drug Authority of Uganda · Program for Appropriate Technology in Health

National Pharmaceutical Control Bureau of Malaysia · National Institute for Drug Quality Control of Vietnam

Medicines Control Authority of Zimbabwe · Organon International

Management Sciences for Health/Rational Pharmaceutical Management Plus Program

Ensuring the Quality of Medicines in Resource-Limited Countries

An Operational Guide

UNITED STATES PHARMACOPEIA
DRUG QUALITY AND INFORMATION PROGRAM

IN COLLABORATION WITH

World Health Organization

National Drug Authority of Uganda

PATH
Program for Appropriate Technology in Health

National Pharmaceutical Control Bureau of Malaysia

National Institute for Drug Quality Control of Vietnam

Medicines Control Authority of Zimbabwe

Organon International

MSH
MANAGEMENT SCIENCES *for* HEALTH
RPM Plus | Rational Pharmaceutical Management Plus

Published 2007.

This publication was made possible through support provided by the U.S. Agency for International Development, under the terms of Cooperative Agreement number HRN-A-00-00-00017-00.

For more information, contact:

U.S. Agency for International Development (USAID)
G/PHN/HN/HPSR
1300 Pennsylvania Avenue, N.W.
Washington, DC 20523-3700 USA

Phone: (202) 712-4789 · Fax: (202) 216-3702 · E-mail: aboni@usaid.gov

United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA

Phone: (301) 816-8162 · Fax: (301) 816-8374 · E-mail: uspdqi@usp.org

Recommended citation:
United States Pharmacopeia Drug Quality and Information Program and collaborators. 2007. *Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide.* Rockville, Md.: The United States Pharmacopeial Convention. Available online: www.usp.org/worldwide/dqi/resources/technicalReports.

Printed in the United States of America

♻ Printed by a Forest Stewardship Council-certified printing plant, with soy-based inks on 50% recycled (and recyclable) processed chlorine-free paper containing 15% post-consumer fiber.

Design and production by Meadows Design Office Inc., Washington, D.C., www.mdomedia.com

CONTENTS

LIST OF FIGURES APPEARING IN THIS GUIDE

ACKNOWLEDGEMENTS

We gratefully acknowledge the comments and contributions of the following people in reviewing this document:

David Lee (Management Sciences for Health/Rational Pharmaceutical Management Plus Program, and Strategies for Enhancing Access to Medicines, USA); Mohan Joshi (Management Sciences for Health/Rational Pharmaceutical Management Plus Program, USA); Thomas Layloff (Management Sciences for Health/Rational Pharmaceutical Management Plus Program, USA); Thomas Moore (Management Sciences for Health/Rational Pharmaceutical Management Plus Program, USA); Krongthong Thimasarn (WHO SEARO, India); Selvete Shuleta (Kosovo Medicines Agency, Kosovo); Andreas Seiter (World Bank); Ans Timmermans (former Consultant, U.S. Pharmacopeia, Thailand); Fabienne Jouberton (Stop TB, WHO–Geneva, Switzerland); Michael D. Green (U.S. Centers for Disease Control and Prevention, USA); Isidro Sia (University of the Philippines, Philippines); James Hopkins (Borderless Action Against Microbes, Kenan Institute–Asia, Thailand); Truls Eriksen (Essential Drugs and Medicines, WHO–Geneva); Stephen Howells (FYFE Global Services, Pharmaceutical Crime Investigation and Training, Australia); Yuta Uchiyama (Japan International Cooperation Agency, Japan); Kazuko Kimura (Kanazawa University, Japan); Keith E. Conerly (Quality Assurance, U.S. Pharmacopeia, USA); Libby Roughead (University of South Australia, Australia); Ricki Orford (PSI Malaria, Kenya); Abayneh D. Tamir (WHO AFRO); Ot Manolin (Food and Drug Quality Control Center, MOH, Lao PDR); Duong Socheat (National Malaria Control Program, Cambodia); Nargis Maqsudova (Drug Information Center, Dushanbe, Tajikistan); Jun Yoshida (WPRO/WHO); Phillip Passmore (ANTARA Medical Supplies Management Sub-Program, NTT Province, Indonesia).

The authors acknowledge the professional guidance and thoughtful contributions from Anthony Boni, U.S. Agency for International Development; Roger Williams, U.S. Pharmacopeia; Enrique Fefer (formerly U.S. Pharmacopeia); David Lee, Management Sciences for Health; Lembit Rägo, Essential Drugs and Medicines Policy, WHO–Geneva; and Libby Roughead, University of South Australia.

Thanks also go to the following who contributed to the design and production of this *Guide:* Marilyn Foster (USP Drug Quality and Information Program) for leading the review and editing the final *Guide;* Milissa McGinnis, Edwin Toledo, Daniel Seyoum, Laura Krech, Meera Ravichandran, and Joyce Carpenter (USP Drug Quality and Information Program) for their thorough review that led to this revision; and Marc Alain Meadows (Meadows Design Office) for graphic design.

The authors appreciate Cindy H. Dubin, Terry Anderson, and Steven B. Kennedy (Steven B. Kennedy & Associates) for the valuable roles they played in producing the first draft of this *Guide*.

The development of this *Guide* would not have been possible without the financial support of the U.S. Agency for International Development.

WRITING GROUP

Souly Phanouvong, Manager, Drug Quality Assurance and Policy Development, United States Pharmacopeia Drug Quality and Information Program, USA

Eshetu Wondemagegnehu, Technical Officer, Quality Safety of Medicines, Essential Drugs and Medicines Policy Department, World Health Organization, Switzerland (retired)

Nancy Blum, Former Director, United States Pharmacopeia Drug Quality and Information Program, USA

Peter Ssali, Acting Director, National Drug Quality Control Laboratory, National Drug Authority, Uganda

Abdelkrim Smine, Team Leader, Drug Regulation Health Authority, Abu Dhabi, United Arab Emirates; formerly United States Pharmacopeia Drug Quality and Information Program, USA

Todd Dickens, Senior Procurement Officer, Program for Appropriate Technology in Health, USA

Eishah Rahman, Director, National Pharmaceutical Control Bureau, Malaysia

Trinh Van Quy, Director, National Institute for Drug Quality Control, Vietnam

Gugu Mahlangu, Director, Medicines Control Authority; Acting Director, Laboratory Services, Zimbabwe

Hugo Vrakking, Technical Advisor, Stop TB Partnership Secretariat, World Health Organization; Technical Officer, Strengthening Pharmaceutical Systems Program,* Management Sciences for Health, Switzerland

Robert Bwire, International Medical Advisor, Drug Safety & Surveillance Department, Organon International, The Netherlands

Annet Bukirwa, Senior Drug Quality Analyst, National Drug Authority, Uganda

Dat Tran, Senior Program Associate, Strengthening Pharmaceutical Systems Program,* Management Sciences for Health; formerly United States Pharmacopeia Drug Quality and Information Program, USA

Kirill Burimski, Senior Program Manager and Technical Advisor, United States Pharmacopeia Drug Quality and Information Program, USA

**Formerly the Rational Pharmaceutical Management Plus Program*

PREFACE

In late 2002, Mr. Anthony F. Boni, Pharmaceutical Management Advisor to 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 (USP) Drug Quality and Information Program led to the development of this publication: *Ensuring the Quality of Medicines in Resource-Limited Countries*. The *Guide* was developed through a collaborative effort among the USP Drug Quality and Information Program; Department of Medicines Policy and Standards of the World Health Organization; 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 USP and USAID to build local capacity in medicines quality assurance and control and in medicines information development and dissemination. USP has worked with USAID since 1992; the partnership now provides technical assistance to more than 25 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 addressing the various problems of ensuring medicines quality in different environments and at different levels—international, regional, national, and local.

Copies of the draft version were distributed to more than 200 individuals, institutions and organizations for use and comment and many of those have responded thoughtfully. This manual, published as a final document, has been revised based on those valuable comments and on the feedback received during the past two years. Though published as final, 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 diseases will be of high quality, no matter where they are produced, procured, distributed, and used.

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

CHAPTER 1

Introduction

Health care professionals and patients assume that the medicines they use are of good quality, but recent reports indicate that substandard and counterfeit medicines are widely available—especially in countries with inadequate regulations and limited regulatory enforcement. This *Guide* is dedicated to the people living without the protection 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 these 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. Households may turn to private medicine retailers and, ultimately, spend a larger proportion of their income on medicines (**World Health Organization, 1999a**).

Beyond immediate health outcomes, using 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 communicable diseases. For example, use of substandard medicines to treat malaria can result in inadequate dosing, allowing the malaria parasite to adapt before it can be eradicated. When a medicine used to treat a disease is no longer effective, a newer medicine is not always available to take its place. When an important medicine is lost to resistance, entire prevention and treatment strategies must be reassessed. The lack of adequate therapeutic response to substandard or counterfeit medicines may lead healthcare providers to prescribe newer, more expensive alternatives, thus placing additional financial pressures on the health care system and the patient. The process of researching and developing new medicines is both lengthy and costly; therefore, ensuring the quality of available medicines becomes more important.

Following the practices listed here will ensure that high-quality medicines are always available:

- Medicine manufacturers use high-quality raw materials and follow current good manufacturing practices.
- Importers and distributors (wholesalers) of medicines store, transport, and distribute according to medicine regulatory agency-approved standards and practices for maintaining product quality.
- Medicine dispensers follow good dispensing practices.
- Medicine regulatory authorities perform their core functions on a regular basis when 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 medicines quality is valued and ensured.

Poor-quality medicines are those that do not meet acceptable standards for strength, quality, purity, packaging, or 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. International organizations and well-established national regulatory agencies have offered guidance on how to address the problem of poor-quality medicines, but few countries are able to allocate the resources and skilled personnel necessary to effectively implement those 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, produce, import, purchase, store, distribute, and use.

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

- Establishing a medicines registration system;
- Monitoring local production of medicines;
- Conducting laboratory testing;
- Performing medicines quality surveillance at peripheral locations;
- Licensing wholesalers and retailers;
- Assuring quality of medicines through procurement, storage, and dispensing operations; and,
- Enforcing regulations.

Aims and Objectives

This *Guide* aims to provide practical advice that countries with limited resources can apply to improve the quality of medicines in their local markets and to ensure that medicines used in their national priority disease programs are of good quality. With this information, program managers, donor organizations, and governments can confidently select, purchase, and

distribute only high-quality medicines, even when limited by human and financial resources, weak infrastructures, and competing priorities. This document does not attempt to address all issues within the pharmaceutical sector, but focuses on the overall process from manufacture to consumer use. It also defines commonly used pharmaceutical terminology to facilitate better communication among all concerned organizations and nations.

The *Guide* can provide a resource for developing tools useful in advancing the many aspects of medicines quality assurance:

- Training courses and materials;
- Product surveillance methodologies;
- Sampling and testing techniques;
- Good laboratory practices;
- Procurement specifications;
- Standard operating procedures;
- Pharmacopeial documents and reference standards.

The *Guide* is founded on six specific objectives:

Objective 1. Offer a tool for national medicines regulatory authorities to evaluate the strengths and weaknesses of existing medicines quality assurance activities and determine how to prioritize corrective actions over time.

- Provide quality control options where gaps currently exist so procurement and distribution can continue with product confidence.
- Provide technical guidance to establish specific components of quality assurance.

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

- Provide unbiased guidance on how to develop procurement specifications, plan for an appropriate selection of products and suppliers, and prepare for both pre- and post-shipment inspections.
- Explain bioavailability and bioequivalence (BA/BE), and recommend when BA/BE data should be required and how to evaluate it for multisource (generic) products.

Objective 3. Provide clear directions to both public and private health care professionals and to retailers regarding the handling and storage of medicines to maintain product stability.

Objective 4. Help governments regulate the local pharmaceutical industry.

- 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.
- Provide references to guidelines for planning and organizing a quality assurance system within a pharmaceutical factory.

Objective 5. Encourage interaction and communication among medicine regulatory authorities, national health program managers, nongovernmental organizations, and manufacturers to resolve problems or conflicts related to licensing, registration, and marketing.

Objective 6. Equip MRAs with the practical means of implementing their existing medicines laws and regulations.

How to Use This Guide

This *Guide* provides a sequential overview of major topics that need to be considered to properly 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; the terms medicine, drug, drug product, pharmaceutical, and pharmaceutical product are used interchangeably. The CD-ROM inside the back cover contains individual PDF files for each separate *Guide* chapter. With both the book and the CD-ROM, the reader can focus directly on the topic of most importance or greatest interest and refer to other chapters as needed.

Chapters 6, 9, and 10 include a self-assessment checklist that can be followed to evaluate existing policies, procedures, facilities, and human resources; it can be used to identify gaps that need to be addressed or improved. For example, if a registration system is weak, additional postmarketing quality surveillance may be necessary. As a medicines registration system develops and becomes more effective, however, less postmarketing analysis may be required. Chapters 4, 5, and 7 offer a general checklist to guide readers through the process of decision-making, designing, and planning a quality assurance/quality control (QA/QC) framework; they illustrate how to implement and improve specific areas, such as premarketing control, laboratory testing, procurement, storage, and distribution. To comprehensively assess the status of QA/QC capacity and performance, readers are directed to Chapter 13, which describes a rapid assessment tool (**Form G**) that will aid decision-makers and implementers to successfully identify, prioritize, and implement the guide.

This *Guide* is available electronically on the following websites:

- United States Pharmacopeia Drug Quality and Information (USP DQI)
  http://www.uspdqi.org or http://www.usp.org/worldwide/dqi/
- World Health Organization Essential Drugs and Medicines Policy
  http://www.who.int/medicines
- Management Sciences for Health Rational Pharmaceutical Management Plus (RPM Plus)
  http://www.msh.org/rpmplus
- Partners for Appropriate Technology in Health (PATH)
  http://www.path.org.

The CD-ROM that accompanies this *Guide* contains additional resource material that provides more specific topical information.

CHAPTER 2

Ensuring the Quality of Medicines: Key Players and Their Responsibilities

Medicines have been essential throughout history for the treatment of illnesses and prevention of disease. Over the course of time, the oversight by government, public and private professionals, and consumers has assured that those medicines are safe and effective.

Quality of Medicines

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 numerous 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 practices (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 GMPs are available from the World Health Organization and from countries with progressive drug regulatory agencies.

Key Players

Figure 2.1 depicts the main players (described below) involved in the supply and control of medicines.

Government leaders and policymakers

National government leaders and policymakers are responsible for defining national medicines policies that cover access, quality assurance, rational use, and other considerations; however, few low- and middle-income countries include quality assurance in their national medicines policies. Many countries that have established quality assurance programs under national policies have met with notable success.

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 because of inadequate legislation or weak enforcement, counterfeit and substandard medicines proliferate (World Health Organization, 1999a).

Legislation and regulation form the foundation of assuring medicines quality. In brief, national leaders and policymakers are responsible for:

- Formulating and updating legislation and regulations to cover all aspects of national pharmaceutical trade and use. Legislation and regulations form the foundation of assuring medicines quality.
- Establishing a national medicines regulatory authority (MRA) that incorporates the medical, scientific, and technical knowledge and skills necessary to control medicines quality.

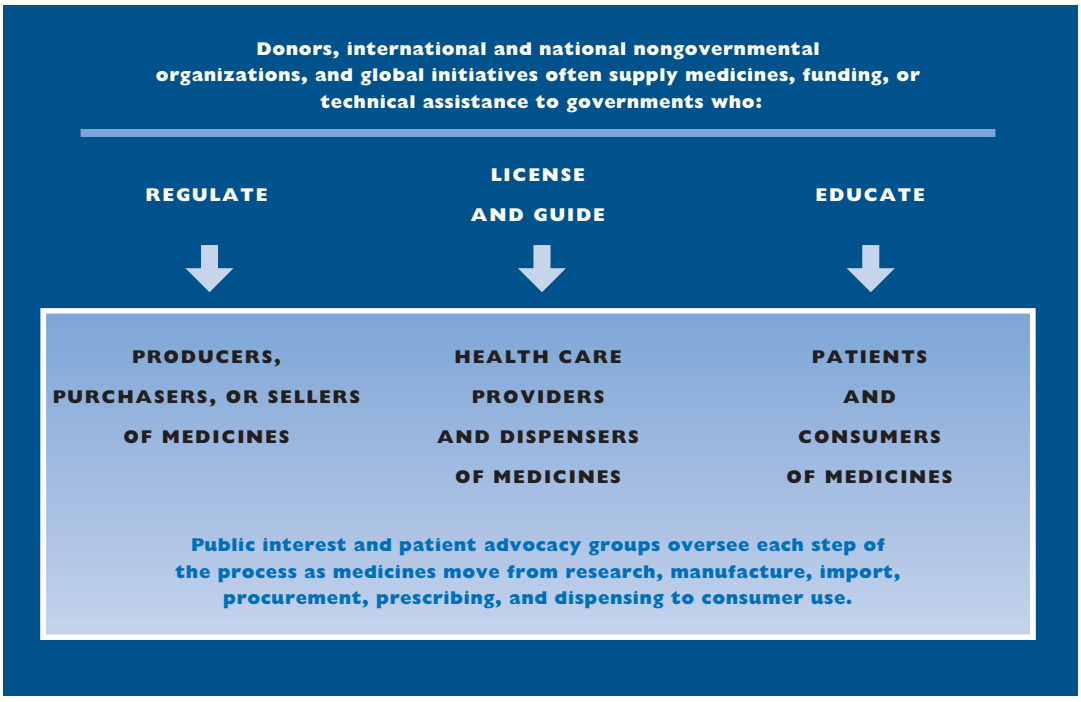


Figure 2.1 Key players and their responsibilities for ensuring medicines quality

For an MRA to function properly, a national government must:

- Enact legislation to empower the MRA.
- Provide appropriate organizational structure.
- Allocate adequate and sustainable financial resources.
- Assign qualified, trained, competent personnel.
- Provide the necessary facilities and tools.

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 entering the marketplace.

National medicines regulatory authorities

MRAs are responsible for ensuring the safety, efficacy, and quality of imported and locally produced medicines. Their authority should encompass both public and private sectors alike. The key activities of an MRA include:

- Registering medicinal products (that is, authorizing the marketing of medicines).
- Licensing pharmaceutical establishments (manufacturers, importers, distributors or wholesalers, and retailers).
- Issuing, amending, and revoking registration for products because of unacceptable quality, safety, or efficacy, including product recall notification.
- Inspecting manufacturing, distribution, and retail premises for compliance with respective guidelines and practices, including GMP, good storage and distribution, and good dispensing practices.
- Performing postmarketing surveillance to secure the quality and safety of medicines in the marketplace.
- Controlling activities designed to promote and advertise medicines.
- Approving clinical trials.

Key points to effectively maximize resources

Countries with limited economic and technical resources may want to prioritize the activities listed below in the following manner to maximize the effectiveness of their resources:

1. License importers, wholesalers, and retailers (pharmacies and medicines outlets/stores).
2. Require registered importers or wholesalers to notify a central body about which products they intend to import or have already imported.
3. Recognize the Pharmaceutical Inspection Cooperation Scheme (PIC/S), International Conference on Harmonization (ICH) guidelines, and WHO prequalification scheme.
4. Perform appropriate evaluation of both multisource (generic) and branded medicines registration. (This topic is explored more fully in Chapter 4.)

Manufacturers of pharmaceutical products

Medicines manufacturers have a variety of responsibilities in ensuring that the products they manufacture are legal, safe, and of acceptable quality. Among their responsibilities are the following:

- Applying for an MRA license to operate.
- Operating under the requirements of the license.
- Assigning or recruiting technically qualified person(s) to oversee quality assurance activities.
- Assuring that the raw materials, including the active pharmaceutical ingredients, excipients, and materials used in production and packaging, have been obtained from reliable sources.
- Manufacturing products in accordance with the current officially recognized good manufacturing practices 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 proper tracking and traceability.
- Establishing a record of complaints and a recall system.

Donors, nongovernmental organizations, and international humanitarian programs

Donors, nongovernmental organizations, and international humanitarian programs play a vital role in advancing the safe and proper use of medicines. They have an opportunity to influence access, rational use, and quality assurance in global, regional, and national arenas and a responsibility to increase access to life-saving and essential medicines for health priority programs. Their mission to help improve the availability, accessibility, and affordability of good-quality, safe, and efficacious medicines while containing the spread of antimicrobial resistance extends to policy, technical, and operational guidance based on their individual areas of expertise as follows:

- Provide funds to country governments and nongovernmental health programs to improve their health care systems.
- Develop legal and policy frameworks and provide guidance to relevant agencies of country governments about how to effectively regulate pharmaceutical sectors and markets.
- Provide technical guidance on the good practices of pharmaceutical manufacture, procurement, storage, and distribution, and on rational use.
- Develop guidelines that address the varied issues in the quality assurance and quality control of medicines and provide technical assistance to national regulatory authorities, health programs, and laboratories to implement them.
- Promote implementation of and adherence to critical international standards and procedures for the quality, safety, and efficacy of pharmaceutical products in all international, regional, and national programs.
- Develop procedures and undertake measures to facilitate international initiatives for medicines procurement in priority health programs.

Procurement organizations, wholesalers, and distributors

The agency in charge of procuring or purchasing medicines is responsible for:

- Holding an authorized license issued by the MRA, if one exists, and operating under the requirements of the license.
- Assigning technically qualified person(s) to oversee quality assurance activities.
- Developing standard operating procedures to guide procurement, including defining specifications of products to be purchased.
- Ensuring that the products they purchase are approved by the MRA.
- 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 storage and distribution practices and MRA requirements.
- Maintaining records of products purchased and distributed, and establishing a product recall system.
- Retaining samples of products procured and distributed.

National disease programs

Personnel in a country's national disease program are responsible for adhering to national health and medicines policies as follows:

- Ensuring that medicines in use are approved by the relevant authority, including the MRA.
- Adhering to the responsibilities listed for procurement organizations if they are involved in the procurement, distribution, and supply of medicines.

Medicines prescribers

Healthcare professionals who prescribe medicines are responsible for doing so according to nationally or internationally accepted standards as follows:

- Informing patients about the proper use of medicines.
- Advising patients to purchase medicines only from licensed retailers.
- Telling patients to report any adverse drug reactions from taking the medicines.
- Reporting any adverse drug reactions to the appropriate authorities.

Medicines dispensers

Because individuals who dispense medicines have direct contact with consumers and patients, they play a vital role in ensuring that 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 the pharmaceuticals.
- Documenting dispensing practices according to national regulations.

Patients, consumers, and patient advocacy groups

Persons who use medicines must also take responsibility for their own health by:

- Purchasing or obtaining medicines only from outlets or health facilities that are properly authorized or licensed to dispense medicines.
- Examining physically and visually the medicines they purchase or receive to ensure that they have received the correct product in the right strength with a current expiry date.
- Ensuring that medicines bear appropriate labeling and instructions regarding their use.
- Following the advice provided by dispensers and physicians, as well as instructions on labels.
- Storing medicines according to the instructions given by dispensers or according to the pharmaceutical label.
- Using only medications or drugs that have not expired or physically changed (e.g., discolored or deteriorated).
- Informing the dispensing outlet or physician if a product has changed in appearance or form.
- Reporting to their doctor if their health has not improved despite therapy or if they have experienced any adverse drug reactions.

CHAPTER 3

Policy and Legal Framework for Ensuring the Quality of Medicines

This chapter describes the purpose, development, and crucial elements of a medicines policy and the legal framework required to implement it.

What Is a National Medicines Policy?

A national medicines policy, a written document that expresses a government's commitment to set goals concerning the pharmaceutical sector, is an integral part of a national health policy. It defines the roles and responsibilities of the main players in both public and private sectors and 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 policies in Bangladesh, Bhutan, Indonesia, Laos, and the Philippines outline the various activities of the pharmaceutical sector in a single, comprehensive document. Other countries have policies that cover particular activities in a system of separate documents (World Health Organization, 2004a).

General objectives

At a minimum, a national medicines policy ought to encompass issues of access, quality, and rational use.

ACCESS

A national medicines policy needs to pay particular attention to the diseases usually associated with poverty, such as malaria, HIV/AIDS, and tuberculosis, and those affecting children

and women. National strategies that finance the supply of medicines must strive to make them affordable for all citizens and design distribution systems to ensure that medicines are available at all levels in the supply chain.

QUALITY

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

RATIONAL USE

Policies for the use of medicines by health professionals and consumers must exist that are therapeutically sound and cost-effective.

ADDITIONAL CONSIDERATIONS

A country's healthcare aims, political priorities, and economic goals determine specific objectives. For example, to ensure regular access, a national government might incorporate in its policy an objective to increase national pharmaceutical production capacity.

Key components

A national medicines policy usually comprises at least nine key components:

SELECTION OF MEDICINES

The choice of medicines to be included in a national medicines policy should be based on the model of essential medicines that promotes equity and establishes priorities for a nation's health care systems. This concept stresses the use of a limited quantity of carefully selected medicines on the basis of accepted therapeutic guidelines. In theory, this concept should lead to a better supply of medicines, rational prescribing, and affordable costs for the majority of the population.

AFFORDABILITY

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

FINANCING MEDICINES

Appropriate and realistic financing will lead to improved access to essential medicines. When considering medicines financing schemes, key issues 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 would include a public-private sector mix in supply and distribution, sound procurement policies, contingency measures for acute emergencies, and a disposal system for unwanted medicines.

REGULATION AND QUALITY ASSURANCE

A national medicines policy must contain a plan to establish a regulatory body that will develop and implement legislation to ensure the quality, safety, and efficacy of medicines. To ensure a sound legal basis and sufficient resources to establish an effective national medicines regulatory authority, governments must be committed to medicines regulation and enforcement.

That authority must have transparent decision-making processes and must be committed to good manufacturing, inspection, and law enforcement practices.

RATIONAL USE

Patients should receive medicines appropriate to their needs, in the right doses, for the appropriate period, and at the lowest cost to them and their community. The importance of promoting rational use through therapeutic guidelines, support for therapeutics committees, and continuing education for health care providers and consumers cannot be understated.

RESEARCH

Operational research is necessary for assessing the effects of a medicines policy on national health care delivery systems and for identifying problems related to medicines 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 EVALUATION

Government commitment to the principles of monitoring and evaluation must be delineated in the national medicines policy, and should be demonstrated by undertaking an independent assessment of the impact the policy will have on the health of the population. The assessment should include indicator-based surveys of the progress and success of the policy.

Legal framework

The mere existence of a written medicines policy does not guarantee its implementation. Qualified human resources and adequate financial resources are also required, as are 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 individual citizens.

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

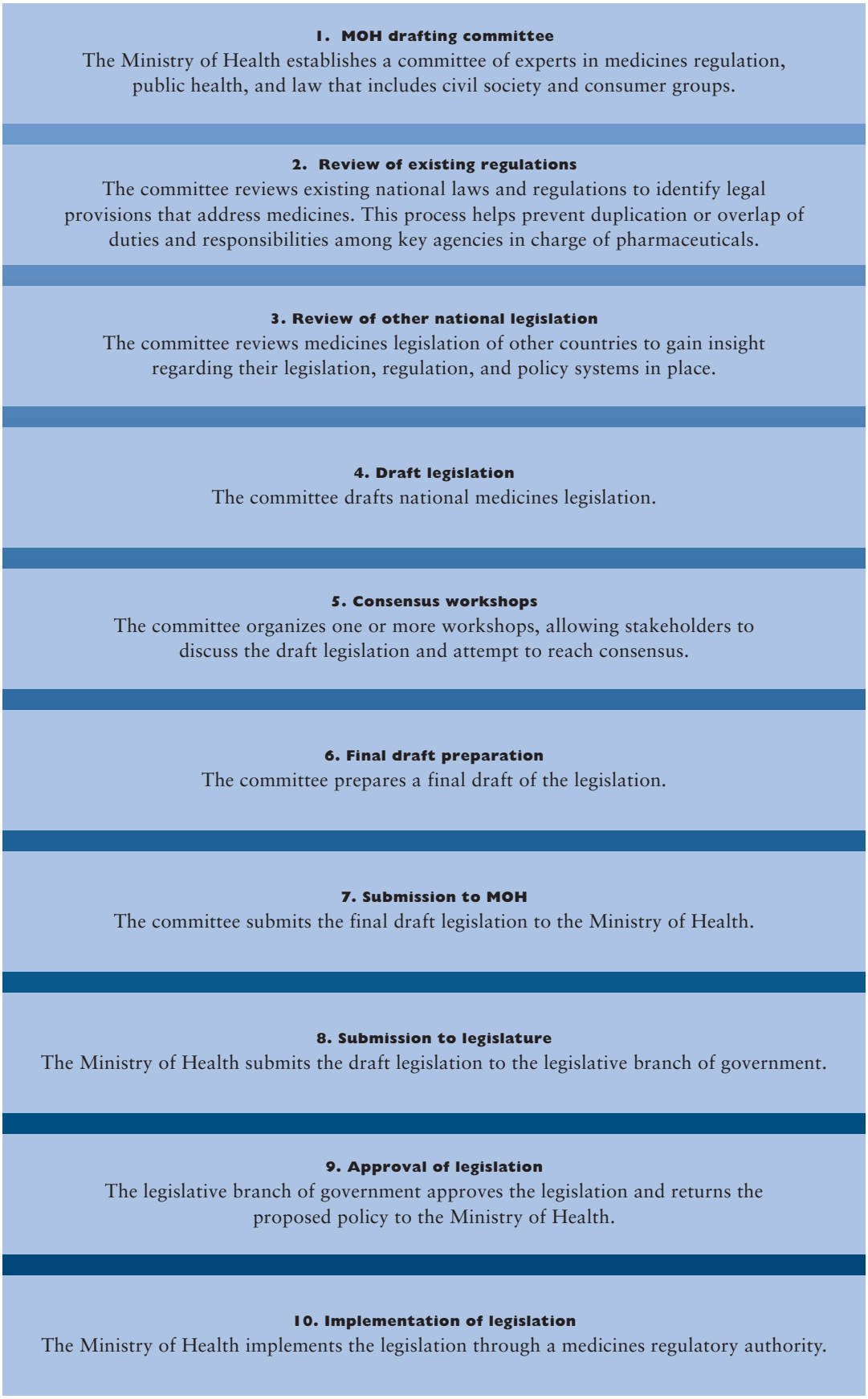
Drafting National Medicines Legislation

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, health care providers, manufacturers, procurement organizations, distributors, civil societies, dispensers, and patients. Participation and ownership will enhance cooperation and collaboration among all parties when the policy is implemented.

Medicines play a substantial role in a country's health strategies, thus the importance of developing the national medicines policy within the framework of the national health policy so that it is consistent with the broader national objectives. Likewise, the health policy, and

Figure 3.1
Drafting process for medicines legislation

The executive branch of government is responsible for health care issues. The process of promulgating national legislation that regulates medicines involves a number of steps, usually including those listed here, though the steps may vary according to individual government systems.



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 the issues, draft legislation, and build consensus. Discussions should include representatives from civic and consumer groups. The final draft legislation can then be submitted to the government for debate, adoption, and enactment.

Content of legislation

Legislation regulating medicines should be comprehensive, incorporating all components of the national medicines policy that a government wishes to oversee. 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 and advertisement.

Medicines legislation needs to 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, sale, and promotion of medicines adhere to such standards until they reach their end users.

Many resource-limited countries, however, cannot ensure the safety, efficacy, and quality of medicines circulating in their markets. In 2003, the World Health Organization (WHO) 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 advancement of technology in import, export, and distribution networks, including e-commerce, increasingly challenges the capabilities of MRAs with limited resources to ensure the safety, quality, and efficacy of medicines.

A checklist for establishing a functional medicines regulatory agency appears at the end of this chapter (Checklist 4.1).

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:

- Evaluating and registering medicinal products.
- Inspecting and licensing manufacturing premises, importing and exporting agents, distributors, and wholesale and retail outlets.
- Conducting postmarketing surveillance.
- Regulating medicines promotion and advertisement.
- 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, 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 (WHO, 1999b).

To support its functions, an MRA must develop appropriate standards, guidelines, and procedures. In the early stages of medicines regulation, MRAs may choose to adapt existing guidelines and procedures for national use that have been developed by other organizations, such as the World Health Organization, Rational Pharmaceutical Management Plus (RPM Plus), and U.S. Pharmacopeia Drug Quality and Information (USP DQI) programs. 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.

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 limited-resource 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 the Malaysia National Pharmaceutical Control Bureau (NPCB), showing its management authorities.

COORDINATION/SYNERGY

Medicine regulatory systems must work in harmony with all functional units within the MRA communicating and coordinating activities. Though this is one of the most difficult practices to establish—even in more advanced MRAs—it is also one of the most important requirements. When a serious quality or safety defect is discovered in a pharmaceutical product, the product must immediately be stopped from additional circulation and recalled, the license of the product owner suspended or revoked, and the product registration may need to be delisted. In this, and in other common regulatory situations, a different MRA unit or official carries out each process. Without harmonization and effective coordination, regulatory actions cannot take place in a systematic or timely fashion, to the detriment of the public health.

OPERATION AND FUNCTION

To function properly, an MRA needs a strategic plan with a clear vision and mission, objectives, strategies and targeted timeframes 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 and regulatory gaps.

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 medicines production, importation, exportation, 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.

Figure 4.1
MRA resource requirements

Source: Adapted from Jayasuriya, 1985.

Resource	Optimal Function
Personnel	■ Regulatory activities (e.g., licensing and registration) ■ Monitoring, inspection, surveillance, and enforcement
Physical 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 collection and analysis ■ Information dissemination
Financial	■ Capital and recurrent expenditures ■ Technical programs ■ Payments for consultants ■ Publications (forms, licenses, pharmacopoeia)

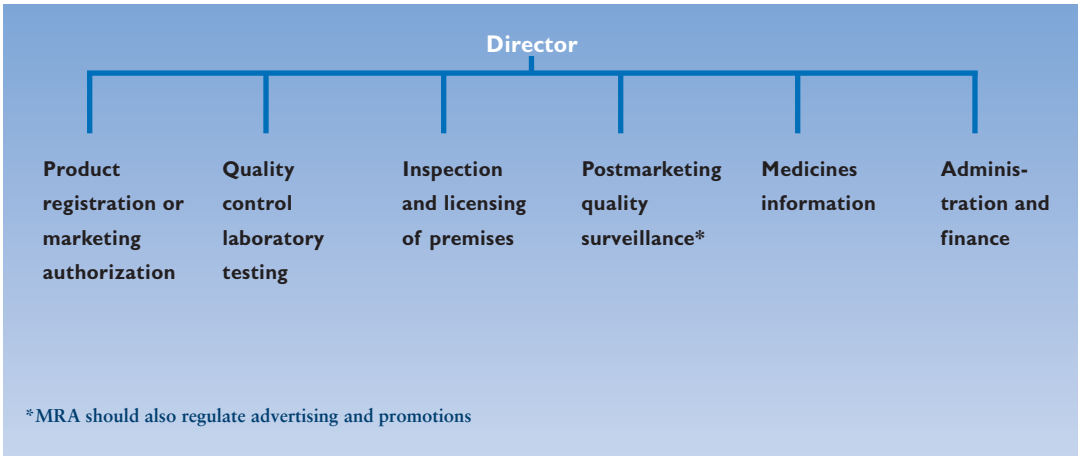


Figure 4.2 Minimum recommended structure for a functional MRA

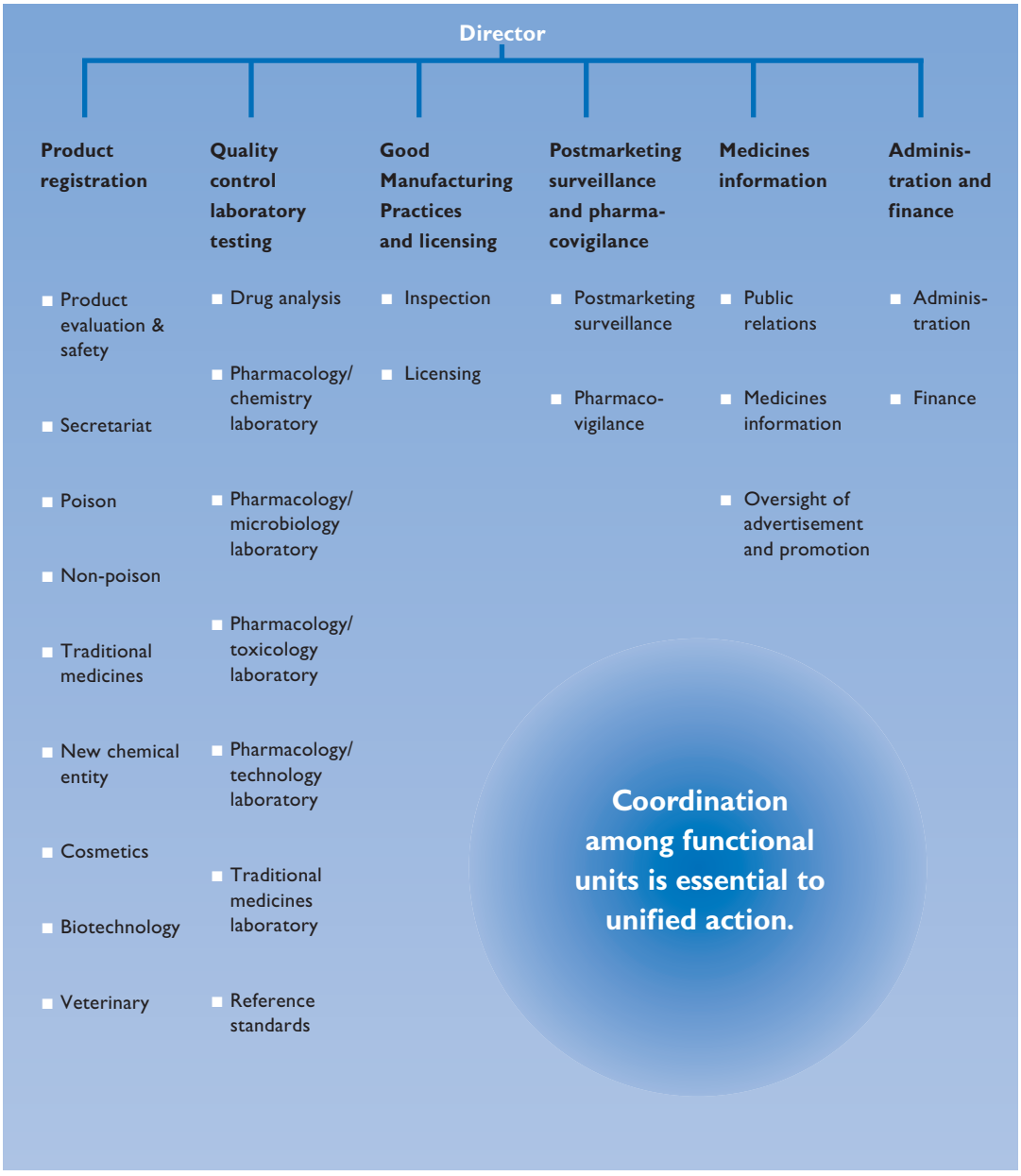


Figure 4.3 Organizational structure of an advanced national MRA

Source: Adapted from National Pharmaceutical Control Bureau, Malaysia, 2003.

Human and financial resources

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

Appropriate levels of human and financial resources are critical for successful medicines regulation. MRAs should employ personnel with specialized knowledge and skills who are not 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 continuing education.

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 generally 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 pose 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. Special considerations, such as fee reduction or fee exemption, however, 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 submitted must be accompanied by 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, however, may 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 the **Malaysia NPCB (2003).**

Fast-track registration

The process of registering medicines in some countries can take from several months to several years depending upon the MRA regulations, system, requirements, and capacity. Other

factors, such as the nature of the application—whether for an innovative or multisource (generic) product—can also affect the registration processing time. To improve timely access to medicines and ensure their availability as well as their quality, MRAs may consider including a provision in their regulation that establishes a "fast track registration" system.

Just as it sounds, fast-track registration speeds up the registration process, allowing certain medicines to be made available more expediently under certain special circumstances:

- Medicines for priority diseases including malaria, tuberculosis, and HIV/AIDS provided through global initiatives (Global Fund to Fight AIDS, Tuberculosis and Malaria; President's Emergency Plan for AIDS Relief; Global TB Drug Facility). An MRA can consider expediting registration of these medicines to ensure continuous supply.
- Products that have been prequalified by the WHO-UNICEF-UN Prequalification Scheme or by an advanced MRA, such as the U.S. Food and Drug Administration, European Agency for Evaluation of Medicinal Products, or Therapeutic Goods Administration of Australia.
- Multisource (generic) medicines that have been evaluated and registered in one or more countries with stringent MRAs.
- "Orphan" medicines for rare and serious or life-threatening diseases through a special access scheme and health care facilities.
- Donated medicines, allowing full registration of the medicines upon receipt in lieu of a formal waiver.

Components of a dossier for MRA evaluation

Applications may be filed to market (1) a new medicine, or (2) a multisource (generic) medicine, including a branded generic product. A new medicine is one that has never before been registered and marketed in the country. A medicine that has been previously marketed in the country for which the dosage form or route of administration has changed can also be considered a new medicine. A generic medicine—identical or bioequivalent to a brand-name drug in active pharmaceutical ingredient (API), dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use—is one that has been promulgated in a specified standard by an MRA (United States Food and Drug Administration, 2005). Generics are 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.

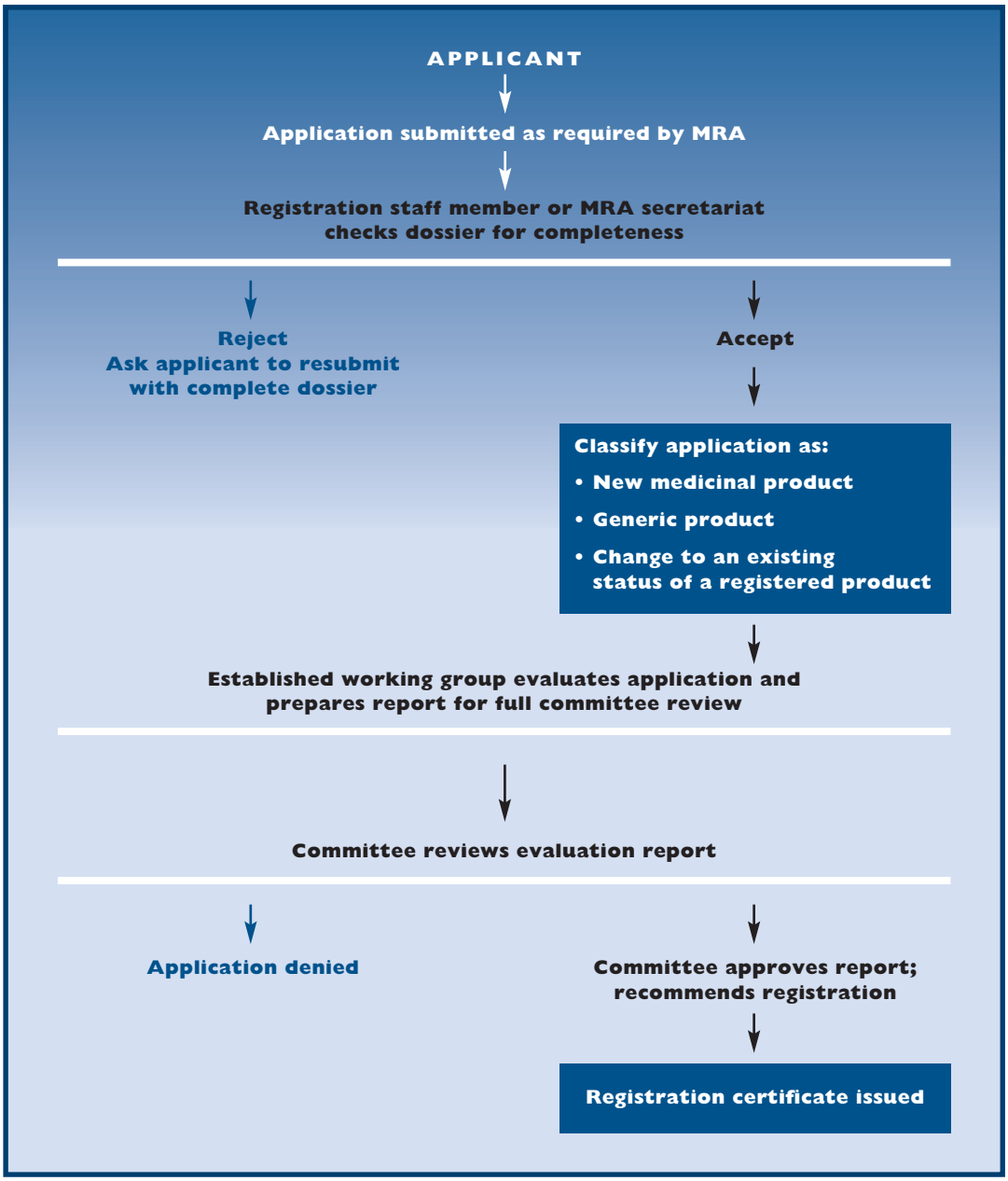
Dossiers of multisource (generic) medicines submitted for MRA evaluation generally contain the information outlined below.

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 that meet current regulations, such as being a registered pharmacist or a pharmacy assistant with at least two years of experience practicing pharmacy; they should also possess adequate financial resources to operate their business. Registration cer-

Figure 4.4
Flow chart of medicines registration

The process of reapplying is determined by the individual MRA.



tificates may not be transferred to another applicant that is not Good Manufacturing Process (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, therapeutic classification, and a brief description of its physical characteristics. The product and the packaging submitted with the dossier must precisely match those described in the dossier.

The labeling on the primary packaging (that is, the packaging that comes in direct contact with the medicine) should conform to technical and regulatory requirements. MRA staff should assess the following information for the sample submitted: language used, international nonproprietary name (INN) or generic name, quantities of APIs, manufacturing and expiry dates, batch or lot number, storage conditions, and name and address of manufacturer. 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 compliance to current good manufacturing practice before the product is registered.

PACKAGING MATERIAL SPECIFICATIONS AND PRODUCT COMPOSITION

The MRA should examine detailed specifications of the primary packaging and closure system and its suitability for the product. The product formula—APIs and inactive excipients—must be provided by the manufacturer. Approved INN names, chemical names, and molecular formulae for APIs must be provided, and reasons for including inactive excipients 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 non-pharmacopeial 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 (1996a). 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 applicant should follow the guidelines of the International Conference on Harmonization.

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). Some medicines—orphan medicines, for example—may not need to be registered, as long as they are used for the treatment of rare and localized diseases, and they are registered in the country of origin with stringent regulation. MRAs with limited regulatory system capacity are encouraged to participate in the WHO Certification Scheme; that would allow them to request information on the legal status of the product being considered for registration from MRAs in other countries.

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 the target population to assess a multisource (generic) product's equivalence with the innovator product are required, and a dissolution profile should be provided. Chapter 12 explains in more detail 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 has changed, should involve the same comprehensive review and evaluation.

Toxicological Studies. 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. 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. 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). 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, European Pharmacopoeia, 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?
- If required, have the documents been authenticated by the proper authorities in the originating country?
- 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.[1] 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 medicines.

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 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:

- Senior clinician from a major teaching hospital
- Pharmacologist from a university or research institute or hospital
- Regulatory personnel from the national MRA
- General or community medical practitioner
- Community pharmacist
- Manufacturing or GMP expert
- Pediatrician
- Representative from consumer groups

Suspension or revocation of product registration

An MRA should have the power to remove deficient products from the market. In doing so, if available information justifies it, the MRA may suspend or revoke registration or marketing authorization for a given product. 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 varying 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 study 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

Most services connected with medicines manufacturing involve inspection, licensing, and control of pharmaceutical manufacturing facilities, 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-limited 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. A sample checklist is provided at the end of this chapter, and more information is available in the references provided at the back of this *Guide*.

Inspection and licensing of medicines distributors

All links in the distribution chain (importers, wholesalers, and retailers) require a license and 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, 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.[2] Inspections may involve an examination of product appearance, expiry date, packaging, package inserts, registration numbers, manufacturing license numbers, name and address of the manufacturer, and other labeling information.

Quality Assessment for Pre-Approval and Postmarketing Surveillance

Pre-approval 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 pre-approval testing.

Postmarketing surveillance

MRAs are advised to monitor the quality and safety of medicines to prevent harmful, substandard, and counterfeit medicines from reaching the public. Numerous reports have been published disclosing evidence of substandard and counterfeit medicines circulating in the markets of many countries. This alarming situation underscores the need for MRAs to quickly introduce intense postmarketing surveillance in strategic sites or, if feasible, throughout the country.

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 for filing product complaints regarding quality should also be instituted. Such complaints should be investigated and documented.

Countries with inadequate medicines registration systems, for instance, those with weak premarketing control, should consider implementing routine postmarketing surveillance of medicines quality for priority health programs, such as malaria and HIV/AIDS. In addition, a national MRA may introduce an intensified monitoring system for targeted products with suspected quality problems.

Product quality can be assessed 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 compendial requirements (e.g., *British Pharmacopoeia*, *U.S. Pharmacopeia*, *International Pharmacopoeia*, etc.) or to manufacturer 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.

Monitoring Adverse Drug Reactions

An adverse drug reaction (ADR) reporting system should be established to monitor medicines safety, and an advisory committee should be established to review ADR reports. One very effective method to acquire and exchange relevant information on medicines safety is networking with other international organizations. Reviewing data collected from various sources provides a firm base for decision-making on appropriate actions to take. Awareness programs to promote ADR reporting among medical and health professionals also should be conducted.

ADR monitoring entails proper reporting, data collection, investigation, and management of adverse reactions. A successful ADR monitoring system requires coordination among all those involved, from patients to health care providers, from regulatory authorities to the central ADR coordinator, from the pharmacovigilance center to safety review experts. Patients are responsible for reporting any adverse reactions to their health care providers, who create the report and enter the data into the ADR database. The data can then be reviewed and analyzed by the advisory committee.

Pharmaceutical manufacturers, having primary responsibility for the safety of their products, must ensure that suspected ADRs to their products are reported to the regulatory authority.

A simple report form and an easy method to turn it in, made available free-of-charge, would encourage patients and health care providers to participate in the ADR program. The form should capture the following essential information:

1. Patient's age, gender, and a brief medical history (if appropriate).
2. Adverse reaction: nature of reaction, localization, and severity; results of any investigations and outcomes (if applicable).
3. Suspected medicine: name (brand or generic listed on label), dose, batch number, dosage form, route of administration, start/stop dates.
4. All other medications used: names, doses, and dosage forms.
5. Risk factors: any medication allergies or other health issues that may impede the proper action of the medicine.
6. Name and address of the reporter (to be considered confidential and to be used only for data verification/clarification and case follow-up).

For more information on how to establish an ADR monitoring system, refer to World Health Organization (WHO) guidelines on the safety of medicines in public health programs (**WHO, 2006a, 2004a**). A sample ADR reporting form is included in the Forms section of this book (**Form A**).

Disseminating Medicines and Poison Information

A 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 medicines 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, databases, certificates, standard operating procedures, 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.

---

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

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

Checklist 4.1
Establishing a functional medicines regulatory agency (MRA)

LEGISLATION, REGULATION, AND POLICY

- ☐ Establish a medicines law to:
  - ▫ Control medicines production, importation, exportation, sale, distribution, and use.
  - ▫ Provide clear and specific provisions regarding sanctions.
- ☐ Enforce laws.
  - ▫ Ensure compliance with the law by all practitioners of medicines production, importation, exportation, sale, distribution, and use.
  - ▫ Authorize the MRA to take punitive actions against violators.
- ☐ Establish regulations governing specific medicines 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 medicines registration and marketing activities.
  - ▫ Inspect and license pharmaceutical establishments, and control production, importation, and exportation.
  - ▫ Establish a quality control laboratory.
  - ▫ Perform postmarketing surveillance for quality and adverse drug reactions.
  - ▫ Control drug promotion and advertisement.
- ☐ 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 medicines 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

☐ Specifications and guidelines:

- 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 dependability 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 to 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, and 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 the Quality of Medicines Through Good Manufacturing Practices

The pharmaceutical industry is responsible for ensuring that manufactured medicines are safe, effective, and of good quality. Regulatory authorities require those medicines to be produced, packaged, and distributed according to current Good Manufacturing Practices (GMP) in an effort to protect the public from potential health hazards of substandard products. To survive in an increasingly competitive global marketplace, manufacturers must invest in technology to produce quality products that meet GMP standards. By complying with GMP, companies not only develop a reliable product, but benefit by gaining public trust, broader (or international) recognition, and additional business opportunities.

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

What Is GMP?

GMP is the part of quality assurance that ensures that medicines 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 of the countries where they intend to manufacture their products. Basic GMP principles are specified by the World Health Organization (1998,

2000c) and the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Many resource-limited countries have adapted the World Health Organization (WHO) GMP guidelines to serve as national standards; they provide a sound basis that pharmaceutical manufacturers can follow to develop their own detailed GMP programs.

Manufacturers are encouraged to strive for GMP in all aspects of their production. By including a GMP policy in their company mission statements, manufacturers demonstrate to employees the company's commitment to producing quality products. One way to assure a reliable medicine is to use active pharmaceutical ingredients (API) that have also been developed in compliance with GMP standards. For more information about GMP for production of APIs, manufacturers can refer to the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.[1]

These core principles drive all good manufacturing practices and form the foundation upon which the WHO guidelines, PIC Scheme, and other regional or national GMP guidelines are grounded, ideals that ensure the following:

- All manufacturing processes are clearly defined, systematically reviewed on the basis of experience, and consistently proven to result in quality pharmaceutical products that comply with established specifications.

- Qualification and validation are performed; that is, that a condition or standard complies with standard GMP requirements for facilities, equipment, and personnel qualification. Validation means conforming to accepted and valid principles and methods regarding manufacturing plans and records, equipment, utilities, facilities, and processes (WHO, 1997c).

- 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; proper storage and transport; and sufficient laboratories and equipment for in-process control.

- Procedures are written clearly.

- Equipment operators are trained to adequately carry out procedures.

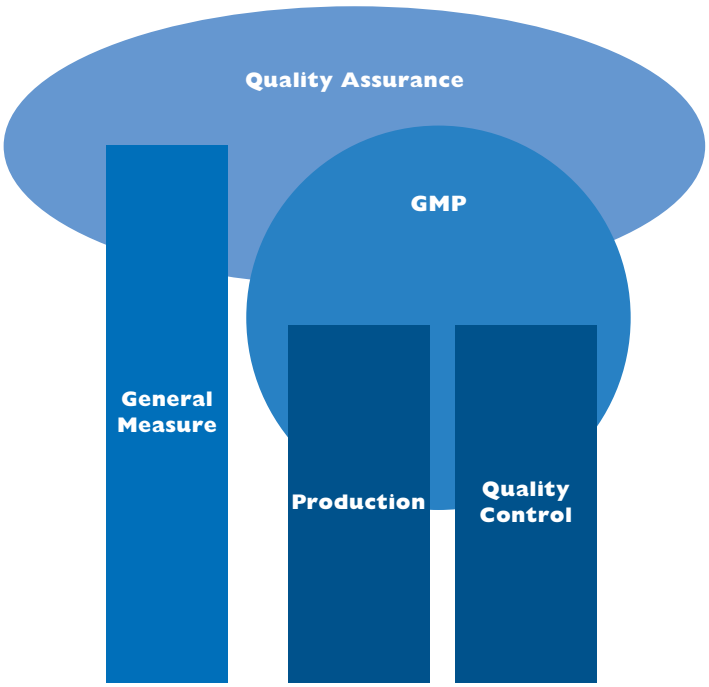
- Adequate manufacturing records are retained—manually or electronically—to prove that the quantity and quality of the product meet expectations, and that any significant deviations are fully documented and investigated.

- Manufacturing and distribution activities are recorded and accessible to provide a complete history of a batch of product, and a system is in place to recall any batch at any time should there be any serious quality defects or life-threatening concerns for safety or efficacy problems. (More information on product recall is available in Chapter 9.)

- Product complaints are examined, quality defects are investigated, and appropriate measures are taken.

Figure 5.1
General interrelationship among quality assurance, quality control, good manufacturing practices, and pharmaceutical production

Source: M. Jahnke, *Quality Assurance Workbook for Pharmaceutical Manufacturers*, River Grove, IL: Davis Healthcare International Publishing, LLC; 2005.



Meeting GMP Requirements

The establishment and implementation of an effective quality assurance program is an essential part of any medicines manufacturing process.[2] Figure 5.1 shows the general interrelationship among quality assurance (QA), quality control (QC), good manufacturing practices (GMP), and pharmaceutical production. Quality assurance covers a broad range of measures; GMP specifically characterizes those activities that guarantee medicines are produced under the constant scrutiny of quality standards (Janke, 2005).

The main responsibility of a manufacturer's quality control or quality assurance unit is to ensure that manufacturing processes comply with GMP requirements. Inevitably, this means making available adequate resources to support various quality assurance activities. Medicines manufacturers often have an independent unit, staffed with specially trained personnel, that is fully dedicated to addressing quality-related matters. Figure 5.2 depicts an elaborated association of QA, GMP, and QC throughout pharmaceutical product development, production, storage, and distribution.

The tasks of a manufacturer's quality unit are many and varied, and may include:

- Establishing the specifications of raw materials, packaging, and products.
- Ensuring that raw materials are properly handled, received, quarantined, stored, and released.
- Collecting and analyzing samples.
- Inspecting manufacturing facilities and processes.
- Organizing a stability program.

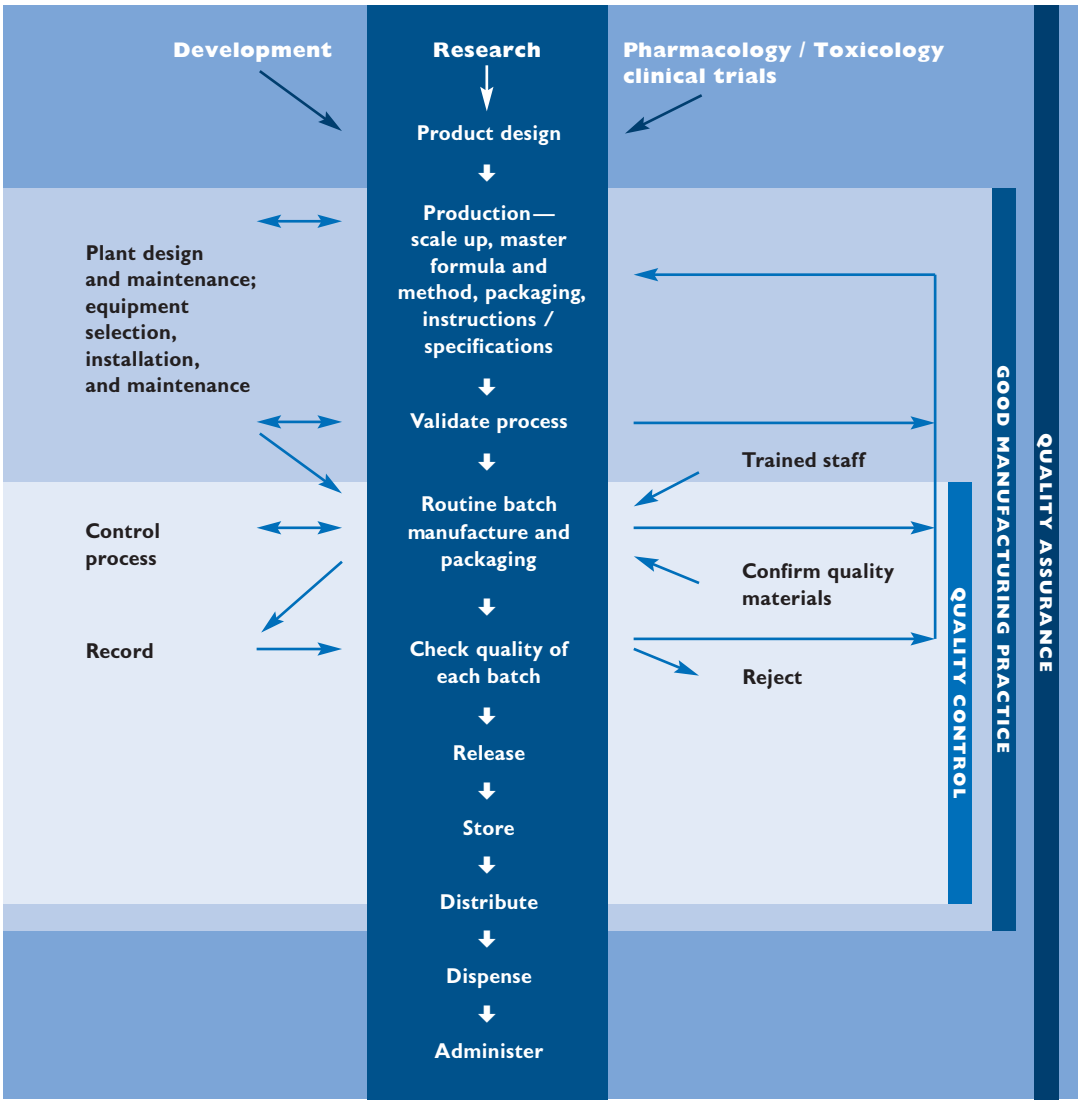


Figure 5.2 Quality assurance and good manufacturing practices

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

- Releasing a medicine to market.
- Managing complaints and recalls.
- Developing and maintaining the documentation system.
- Verifying the integrity of data, whether collected manually or electronically.
- Establishing procedures for conducting regular internal audits and inspections.
- Training employees on GMP programs.
- Acting as liaison between manufacturer and regulatory authorities.

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

Complying with GMP in resource-limited countries

Local medicines manufacturers in settings with limited resources usually operate under difficult conditions with tight budgets. Organizing and establishing a quality unit takes a significant financial, logistical, and organizational commitment. Pharmaceutical manufacturers, despite

Principles and Duties of Quality Control

QC deals with independent quality assessments of materials and stock based on the (mainly analytical) judgment taken, and/or the examination of submitted documents that have been presented. QC is not limited to laboratory work, but is also involved in all decisions that influence product quality.

QC should be organized and established independently from production. The principle duties of QC ensure that:

- Requirements of Good Laboratory Practice (GLP) are followed;
- Every procedure is sufficiently recorded;
- Tests are set up and carried out; and,
- Suitable (analytical) methods for product examination are used.

Moreover, the Quality Control Manager (Qualified Person [QP]) monitors the release of stocks, intermediates, and final products throughout the process.

Source: M. Jahnke, *Quality Assurance Workbook for Pharmaceutical Manufacturers,* 2005.

limitations, must adhere to basic GMP principles even if their focus is meeting the needs of the local market. In areas with these conditions, there is often a high prevalence of infectious diseases, which if treated with substandard medicines, may introduce resistance that could result in dire consequences for both local and global public health. This, in itself, is reason enough to encourage adherence to GMP.

From an economic point of view, it makes good sense for manufacturers to embrace GMP principles. Many leading nongovernmental and international organizations that procure pharmaceuticals (e.g., the Global Fund to Fight AIDS, Tuberculosis and Malaria; the World Bank; UNICEF; and the Global TB Drug Facility) now require their products be obtained only from internationally recognized, GMP-compliant suppliers (United Nations Development Programme, 2005). Some local pharmaceutical companies already produce medicines using high standards of quality, which demonstrates their ability to manufacture under GMP guidelines. Often, instituting simple procedures may be all that is required for a manufacturer to meet GMP compliance.

This tenet applies equally to large and small pharmaceutical manufacturing operations. For example, even small manufacturers can make sure that the buildings used to produce medicines are clean and protected from outside elements (wind, dust, temperature extremes). All medicines producers can validate the identification and purity of active pharmaceutical ingredients before using them.

Standard operating procedures can be drafted on all basic and critical manufacturing processes and implemented accordingly. Instructions can be written clearly, simplifying complex operations and making procedures more easily understood by employees. Pharmaceutical companies can consult WHO GMP guidelines that specify which manufacturing activities require standard operating procedures.

Benefits of GMP compliance

Local pharmaceutical manufacturers that abide by basic GMP principles can benefit from more than the satisfaction of creating quality products that ensure patient safety. Other benefits include the following:

- Competent production, handling, and distribution lead to cost savings, improvement in efficiency, and an increase in profitability.
- Prevention, identification, and resolution of quality problems in a timely manner avert recalls and other punitive actions.
- Greater manufacturing consistency leads to better product quality. Consumers who have confidence in a company's products will become repeat customers.
- A sound local reputation and technical credibility may lead to regional or international recognition.
- Governments often protect local manufacturing business by offering subsidies and repeat procurement to GMP-compliant companies.
- More international business opportunities exist with global organizations that procure only from companies that conform to GMP standards.

Obstacles to GMP compliance

Although some resource-limited countries have made major efforts to develop operational medicines regulatory authorities, weak regulations still exist that stymie their effectiveness. Without strong regulation, manufacturers may not feel obligated to produce high-quality pharmaceutical products. Without pressure from a public aware of the dangers of using substandard medicines, medicines policymakers may not feel obligated to develop or enforce effective regulation. Local manufacturers also face other challenges that keep them from complying with GMP:

- Though stringent rules are necessary, the more costly and time-consuming fees or procedures they require may deter pharmaceutical manufacturers from complying with GMP. For example, regulators may require manufacturers to provide bioavailability/bioequivalence (BA/BE) study results, studies that they cannot perform, with medicines applications. (Chapter 12 discusses bioavailability and bioequivalence studies.) Yet through cooperation with multinational organizations, such as the World Health Organization, simplified screening protocols can be developed to provide specific guidance to manufacturers and medicines regulatory authorities regarding bioavailability testing and medicines registration requirements.

- Some large pharmaceutical companies have subsidiaries in resource-limited countries, but they are generally small operations that produce essential generic medicines by adding value to imported active ingredients. Most local manufacturers are usually small businesses, such as hospital-based manufacturing sites that produce liquid dosage forms or fluids. While these ventures may not require large quality assurance units, neither does their small-scale nature 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 is a cascade of processes that are critical to the quality of the end product.

Identifying and addressing these critical points is an important step in meeting GMP. (For additional information, see World Health Organization, 2003a.)

- Setting up a quality assurance system can be very costly, requiring investments in adequately training QA personnel, building an acceptable program, and possibly necessitating the upgrade or purchase of equipment or facilities. A pharmaceutical company not committed to quality assurance and GMP, facing what seem to be daunting expenses, may choose to sidestep the rules or perform only cursory changes.
- Problems caused by a lack of skilled QA personnel in the manufacturing process might be compounded by the absence of QA technical experts at the national level to offer sufficient guidance.

Strengthening medicines quality through GMP compliance

Sensitizing governments, the public, and pharmaceutical manufacturers to the benefits of producing good-quality medicines is not an easy undertaking; it requires a partnership among the public, national governments, domestic medicines manufacturers, and multilateral organizations. The following recommendations can promote a move toward compliance with GMP standards in resource-limited settings:

- Medicines regulatory agencies can assess the present state of GMP compliance by conducting a comprehensive GMP inspection to identify weaknesses, strengths, and gaps.
- Countries can obtain support from other countries or multinational organizations with GMP experience via bilateral or multilateral agreements.
- Countries can adopt a GMP standard where one is lacking or adapt accepted international standards.
- Countries can pass legislation that makes GMP compliance mandatory.
- Medicines regulatory authorities can monitor GMP compliance at manufacturing sites.
- Governments and trade associations can encourage medicines manufacturers to set up a quality assurance system. Rather than an impediment to manufacturing, GMP principles are based on sound scientific judgment, which, if followed, make good business sense.
- Regulatory agencies can make medicines manufacturers aware of GMP inspections and the consequences of noncompliance, possibly by disseminating information to manufacturers on a regular basis.
- Medicines manufacturers can pursue and obtain quality certification from the World Health Organization or PIC Scheme; regulatory authorities should have a mechanism in place to ensure that manufacturers do not misuse certification. For more information, see the guidelines to the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (1996b) and Forms B, C, and D.
- Medicines regulatory authorities and manufacturers can communicate regularly through meetings, newsletters, or other useful channels.

Principles and Duties of Quality Assurance

Having defined the principles and duties of pharmaceutical production and QC in accordance with the European Community (EC) Manual of Good Manufacturing Practice for Drugs, the following assignments ensure a thorough QA system in cooperation with pharmaceutical production and QC management:

Personnel

- Organization schemes
- Training
- Hygiene requirements
- Staff in key positions
- Job descriptions

Premises and Equipment

- Definition of requirements
- Definition of production, warehouse, and additional areas
- Equipment

Quality Management System

- Definition of general requirements
- Specifications
- Documentation
- Manufacturing and inspection protocols
- Storage and retrieval
- Organization of the Quality Manual (QM)

Contract Manufacturing and Inspection

- Drug contract manufacturing contracts to be defined, agreed upon, and controlled
- Confidentiality agreements
- Establishing responsibility between customer and contractor
- Responsibility and delimitation requirements
- Manufacturing requirements (Technology Transfer)
- Analytical requirements (Analytical Methods Transfer)
- Batch documentation
- Manufacturing according to registered procedures

Complaints and Product Returns

- Dealing with and settling complaints

Self-Inspections

- Introduction, coordination, and pursuit of steps for corrective actions
- Looking after and dealing with internal and external audits

Source: M. Jahnke, *Quality Assurance Workbook for Pharmaceutical Manufacturers*, 2005.

- Medicines regulatory authorities can establish and invoke punitive measures for manufacturers that do not conform to GMP; actions against violators (e.g., recall, withdrawal, revocation, of registration and licenses) can be made public using available media.
- Procurement agencies and hospitals should be required to purchase medicines from only GMP-conforming manufacturers whose names are part of the public record or can be made available through the media.
- Large multinational companies can create an environment in which appropriate technology, human, equipment, and technical know-how might be transferred to local subsidiaries in resource-limited countries to improve access to essential medicines not available in the local market.
- Quality assurance personnel associated with the medicines regulatory authority and manufacturer internal audits can participate in regular GMP training.
- Manufacturers can institute continuing education programs for GMP training and make them available or mandatory for QA employees.
- Regulators, manufacturers, and other interested parties in countries with limited resources can become involved in international decision-making about quality standards by keeping abreast of changes in GMP guidelines as they evolve. Likewise, they can find or create appropriate forums to articulate how those changes will affect their unique domestic or regional situations.
- Universities can incorporate GMP training modules into pharmacy curriculum.
- The public can be educated and empowered to make informed decisions about obtaining quality medicines from reliable sources, via radio programs or health care volunteers.
- Leaders in the field can encourage fellow healthcare professionals to form civil associations that promote use of quality assurance systems.

---

1. ICH Q7A—Good manufacturing practice for active pharmaceutical ingredients, 10 November 2000. Also available online from the official ICH website: www.ich.org.
2. 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 a Government or MRA:

- ☐ Provide national legislation and regulations for controlling pharmaceutical production.
- ☐ Establish good manufacturing practice guidelines.
- ☐ Promote compliance with current GMP guidelines for medicines production by regulation.
- ☐ Enforce compliance with current GMP guidelines by all medicines manufacturers.

For Manufacturers:

OPERATIONS AND PRACTICES

- ☐ Establish a quality assurance unit to perform routine internal GMP audits.
- ☐ Establish key functions for quality control and assurance:
  - ▫ 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 processes.
  - ▫ Conduct review of 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:
  - ▫ Write a defined job description for each position.
  - ▫ Place at least one pharmacist in charge of manufacturing each dosage form production unit.
  - ▫ Assign at least two responsible pharmacists to oversee quality assurance and quality control in small-scale manufacturing plants.
  - ▫ Assign at least two responsible pharmacists or chemists in quality control laboratories.
  - ▫ Require employees to participate in all current training on standard operating procedures and batch record keeping.
  - ▫ Adhere to current GMP regulations and guidelines.
  - ▫ Assign a qualified person to specific equipment or production processes.
  - ▫ Establish continuing training and a training record for each employee.
  - ▫ Periodically review each employee's performance (Control Quest, 2002; Huber, 1998,2001).

TECHNOLOGY AND EQUIPMENT

- ☐ Use appropriate technology and equipment to manufacture medicines.
- ☐ Maintain manufacturing and quality control equipment according to current standards.
- ☐ Ensure validation activities.

- ☐ Validate process (FDA, 1996):
  - 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 cleaning agent
- ☐ Validate utilities:
  - Purified water
    - Water source routinely sampled and tested for compliance with regulatory requirements
    - Major contaminant groups (particulates, inorganics, organics, and microbes) removed
    - Samples collected at least weekly at sampling points and point-of-use ports, and tested for quality based on acceptance criteria
    - Test data records maintained for trends
  - Air handling
    - Rooms for production of medicinal product equipped with air handling unit in accordance with GMP requirements
    - Air monitored for controlled environments requirement of particulate measuring
    - Filters tested for leaks and efficiency
    - Pressure differentials maintained for clean rooms and controlled environments requirement
    - Air flow speed, uniformity, and pattern recorded
    - Environment monitored for particles, microorganisms, temperature, and humidity
  - Compressed air
    - Adequate prefinal filter for compressed air unit in accordance with GMP requirements
    - Pipe constructed with suitable materials
    - System monitored for possible contamination (oil, water, particles, bio burden)
    - Air flow direction labeled at any point
    - System in place to monitor leakage, filter integrity, and pressure control
- ☐ Validate facility:
  - Verify facility design to ensure:
    - Logical flow of materials and personnel
    - No mix-up or cross-contamination

- Sufficient space for operation and maintenance of equipment
- Facility cleanliness

- Verify construction to ensure:
  - As-built facilities conform to design drawings
  - Construction materials meet specifications
  - Equipment installed as planned
  - Utilities routed as planned
- Verify operation and performance to ensure:
  - Facility supports the manufacturing process
  - Facility meets cleanliness specifications
  - Production of three successful consecutive batches using qualified materials, equipment and utilities, and methods validated

DOCUMENTATION

☐ Establish a documentation system that maintains an inventory of all required documents and records.

☐ Review manufacturing and control documents so that:
- 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

STORAGE

ORGANIZATION AND QUALITY MANAGEMENT

☐ Is there a defined quality structure?

☐ Is there a quality policy?

☐ Are all personnel responsibilities clearly defined?

☐ Is a person assigned to every distribution point?

☐ Have job descriptions been established for all employees?

PERSONNEL

☐ Is there an adequate number of qualified personnel to achieve pharmaceutical quality assurance objectives?

☐ Have all personnel received proper training in relation to good storage practice, regulations, procedures, and safety?

☐ Have all members of the staff had been trained in personal hygiene and sanitation? Do they observe high levels of hygiene and sanitation?

☐ Do all personnel employed in storage areas wear suitable protective or working garments appropriate for the activities they perform?

PREMISES AND FACILITIES

Storage areas

- ☐ Have precautions been taken to prevent unauthorized persons from entering storage areas?
- ☐ Are storage areas of sufficient capacity to allow the orderly storage of the various categories of materials and products, namely: starting and packaging materials; intermediates; bulk and finished products; products in quarantine; and released, rejected, returned, or recalled products?
- ☐ Have storage areas been designed or adapted to ensure good storage conditions? In particular, are they clean and dry and maintained within acceptable temperature limits?
- ☐ Are storage areas clean and free from accumulated waste and vermin?
- ☐ Is there a written sanitation program available indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas?
- ☐ Is there a written program for pest control?
- ☐ Are the receiving and dispatch bays designed and equipped to protect materials and products from the weather?
- ☐ Are reception areas designed and equipped to allow containers of incoming materials and pharmaceutical products to be cleaned, if necessary, before storage?
- ☐ Are rejected materials and pharmaceutical products identified and controlled under a quarantine system designed to prevent their use until a final decision is made on their outcome?
- ☐ Are narcotic drugs stored in compliance with international conventions, and national laws and regulations on narcotics?
- ☐ Are broken or damaged items withdrawn from usable stock and separated?
- ☐ Do storage areas provide adequate lighting to enable all operations to be carried out accurately and safely?

Storage conditions

- ☐ Are storage conditions for pharmaceutical products and materials in compliance with the labeling, which is based on the results of stability testing?

Monitoring of storage conditions

- ☐ Are recorded temperature monitoring data available for review?
- ☐ Are temperature registers available?
- ☐ How long are the data kept?

- Are the equipment used for monitoring checked at suitable predetermined intervals and the results of such checks recorded and retained?

DOCUMENTATION

- ☐ Are written instructions and records available that document all activities in the storage areas, including the handling of expired stock?
- ☐ Does permanent information, written or electronic, exist for each stored material or product indicating recommended storage conditions, any precautions to be observed, and retest dates?
- ☐ Are records kept for each delivery?

LABELING AND CONTAINERS

- ☐ Are all materials and pharmaceutical products stored in containers that do not adversely affect the quality of the materials or products concerned, and that offer adequate protection from external influences? In some circumstances, this could include bacterial contamination.
- ☐ Are all containers clearly labeled with at least the name of the material, the batch number, the expiry date or retest date, the specified storage conditions, and reference to the pharmacopeia, where applicable? Unauthorized abbreviations, names, or codes should not be used.

RECEIPT OF INCOMING MATERIALS AND PHARMACEUTICAL PRODUCTS

- ☐ Is each incoming delivery checked against the relevant purchase order and each container physically verified, e.g., by the label description, batch number, type of material or pharmaceutical product, and quantity?
- ☐ Is each consignment examined for uniformity of the containers? If the delivery includes more than one batch, should it be subdivided according to the supplier's batch number?
- ☐ Are containers carefully inspected for possible contamination, tampering, and damage?
- ☐ Are measures being taken to ensure that rejected materials and pharmaceutical products cannot be used?

STOCK ROTATION AND CONTROL

- ☐ Is periodic stock reconciliation performed by comparing the actual and recorded stocks?
- ☐ Are stock discrepancies investigated as a check against inadvertent mix-ups and/or incorrect issue?

CONTROL OF OBSOLETE AND OUTDATED MATERIALS

- ☐ Are all stocks checked regularly for obsolete and outdated materials and pharmaceutical products? Are all due precautions observed to prevent the issue of outdated materials and pharmaceutical products?

RETURNED GOODS

- ☐ Are returned goods, including recalled goods, handled in accordance with approved procedures?

DISPATCH AND TRANSPORT

- ☐ Are materials and pharmaceutical products transported in such a way that their integrity is not impaired and that storage conditions are maintained?
- ☐ Are there procedures for transport?
- ☐ Are devices used to monitor conditions, such as temperature, during transportation?
- ☐ Are devices calibrated?
- ☐ Are the dispatch and transport of materials and pharmaceutical products carried out only after receipt of a delivery order?
- ☐ Are there dispatch procedures established and documented, taking into account the nature of the materials and pharmaceutical products concerned and any special precautions taken?
- ☐ Are records for dispatch retained for at least one year after the stated expiration date?

CHAPTER 6

Ensuring the Quality of Medicines Through Procurement

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. The resulting inefficiencies and waste may be overcome or minimized within a country, or with the assistance of a nongovernmental or donor organization (see Chapter 7), following the recommendations listed here.

Procurement plays an important role in ensuring that quality medicines are supplied to the health care system. 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 medicines and medical supplies in accordance with national and, if applicable, donor procurement regulations. This chapter reviews the objectives of a procurement system; depicts the resources required to operate and maintain an effective procurement system; and describes the procurement process and key activities, procedures, and documentation that a procurement office can use to obtain good quality products.

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 costs.

To successfully achieve these objectives, a procurement unit must work closely with other personnel in the product management cycle—supplier, distributor, customer (Figure 6.1). The procurement 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 requires four essential resource components:

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

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

Operational resources. Adequate office space and proper equipment to maintain operations and current information about suppliers and products.

System resources. A written procurement policy that identifies a transparent selection process and evaluation procedures, documentation requirements, and government procurement regulations.

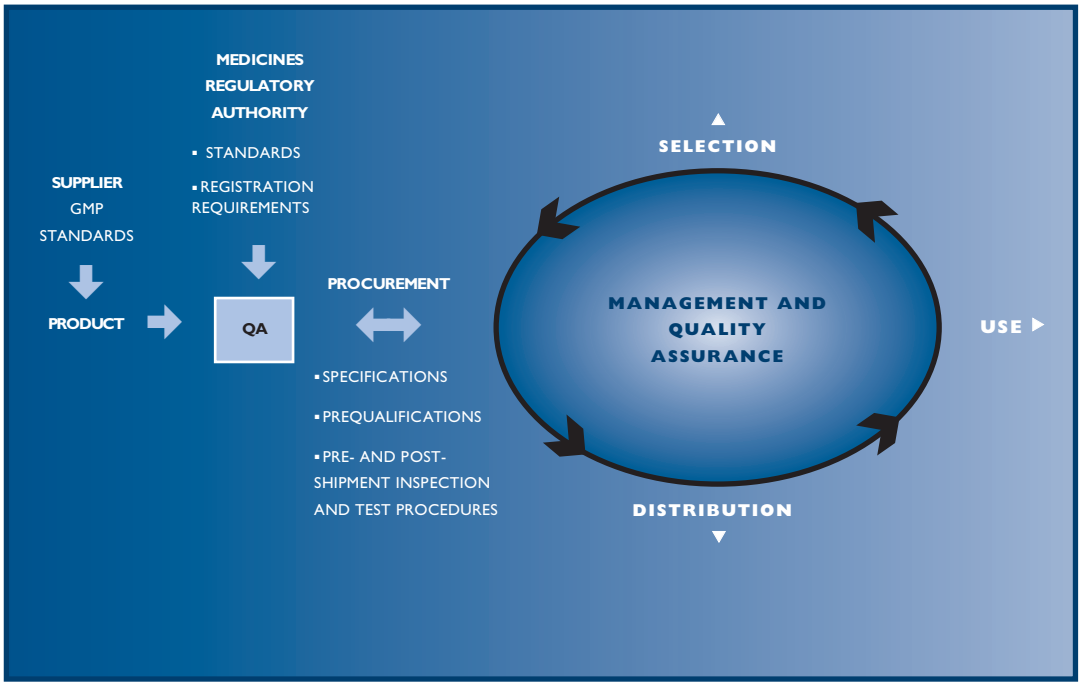


Figure 6.1
Product management cycle

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

The Procurement Process: Ensuring Quality Medicines

The procurement process comprises a series of activities designed to obtain good-quality medicines at the right time, in the right quantities, and at favorable costs (Figure 6.2). 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 remain the same:

- Select products.
- Determine product quantity.
- Prepare technical specifications.
- Identify candidates and select qualified suppliers.
- Prepare and release bidding documents.
- Receive and evaluate bids.
- Award contract.
- Inspect products pre-shipment.
- Receive and inspect products.
- Monitor supplier performance and product quality.

The sequence of activities presented in the list above reflects a more traditional procurement process; more often, a number of activities are conducted separately, but within the same timeframe. For example, Ministry of Health program staff can determine the quantity of medicines needed, while technical staff develop procurement technical specifications. 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 usually handled by separate groups (individuals, committees, subcommittees), and the procurement office coordinates the technical information and expertise each group provides. Figure 6.2 depicts a summary of quality assurance in a more traditional procurement process. Additional procurement options are discussed at the end of this chapter on page 74.

Select products

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 is in place and whether it is supported by a functional medicines regulatory authority (MRA).

At the national level, the Essential Medicines List (EML) is one source of information that may be available even in countries that do not have a functional MRA. The procurement office would first review the EML to confirm that the medicines being requested appear on the list.

Another source of information might be standard treatment guidelines, generally developed for hospitals, for regional or national use, and for disease control programs. These

Figure 6.2
Quality assurance of traditional medicines procurement process

Medicines regulatory authority

SUPPORTING AGENCY	FUNCTION	RESPONSIBILITIES
Drug and therapeutic committee	**Select products**	■ Determine requirements ■ Essential Medicines List ■ Formulary list ■ Standard treatment guidelines
Health care programs	**Determine product quantity**	■ Consumption method ■ Morbidity method
Product selection committee	**Prepare technical specifications**	■ Product information requirements ■ Certification requirements ■ Pharmacopeial standards ■ Labeling requirements ■ Packaging requirements
Supplier prequalification committee	**Identify candidates and select qualified suppliers**	Prequalification ■ Product registration ■ WHO Certification Scheme ■ Supplier questionnaire ■ Reference checks ■ Site inspection ■ Targeted lab testing ■ Supplies of prequalified medicines
Contracts office	**Prepare and release bidding documents**	■ Invitation to bid ■ Technical specifications ■ Conditions of contract ■ Delivery requirements
Bid evaluation committee	**Receive and evaluate bids**	■ **Prequalification** *Limited bidding—compliance with contract and delivery requirements* ■ **Postqualification** *Open bidding—similar to prequalification, but more suppliers to screen*
Contracts office	**Award contract**	■ Contract terms ■ Technical specifications ■ Quality assurance requirements
Inspection agency	**Inspect product before shipment**	■ Inspection requirements in contract ■ MRA or independent contractor performs inspection
Warehouse personnel of qualified laboratory	**Receive and inspect products**	■ Documentation review ■ Inspection of exterior packaging ■ Inspection of product ■ Laboratory testing
MRA and purchaser	**Monitor supplier performance and product quality**	■ Supplier performance ■ Product quality

guidelines help practitioners determine appropriate treatments; they also identify the medicines recommended for treatment, which in most cases are selected from the EML.

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.

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.

In countries that have an effective national medicines 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.[1] An effective national medicines policy will usually result in the development of an EML that satisfies the health care needs of the majority of the population. In countries that have established an EML, products for national health care programs would be selected from those that have been registered by the MRA and appear on the EML.

The national medicines selection or formulary committee, should one exist, screens 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 no such committee exists, the procurement office would work directly with the MRA to establish an information exchange system that allows it to learn whether requested products have been officially registered with the MRA.

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

Product registration and the procurement process operate independently of one another. While any product can be registered at any time in the procurement process, it must be registered with the MRA before it can be released for long-term program use.

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.

Whether or not a 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.

Determine product quantity

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 medicines required. It then contacts all potential program managers to ensure that no disease program has been overlooked. The procurement office also advises program managers of the estimated procurement lead time, that is, the time from receiving requests to medicines delivery, to ensure that requirements are submitted and received in a timely manner. The procurement office then organizes medicines requirements into the largest possible quantities to attain the most favorable prices and contract terms from suppliers.

When submitting their request, the procurement office must list the medicines 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

Establishing clear, well-defined technical specifications 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 identify the requirements with which a supplier must comply and the related supporting documentation that a supplier must provide. For pharmaceutical products and medicines, technical specifications will typically include the following requirements:

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

PRODUCT INFORMATION REQUIREMENTS

Product or medicine information requirements include data on active pharmaceutical ingredients (API), dosage forms, finished product specifications, pharmacology, stability testing, and other pertinent information. If suppliers have been prequalified,[2] most of this information will already have been obtained and evaluated.

The procurement office works in concert with technical personnel to determine what type of documentary evidence should be requested in technical specifications. For example, technical specifications denote the amount of shelf-life remaining when a medicine arrives in a country:

- 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 already will have been reviewed by the committee responsible. This includes prior review of the "Certificate of Pharmaceutical Product" (see **Model Form B**) and "Statement of Licensing Status of a Pharmaceutical Product" (see **Model Form C**) provided under the WHO Certification Scheme (World Health Organization, **1994, 1997b**).

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

PHARMACOPEIAL STANDARDS

Where applicable, the technical specifications will need to state that all products supplied are 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 (equivalent to that found in the product dossier) must be submitted for review.

LABELING REQUIREMENTS

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

PACKAGING REQUIREMENTS

Proper packaging protects a product during transport and extreme weather conditions, thereby maintaining product quality. The technical specifications would 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.

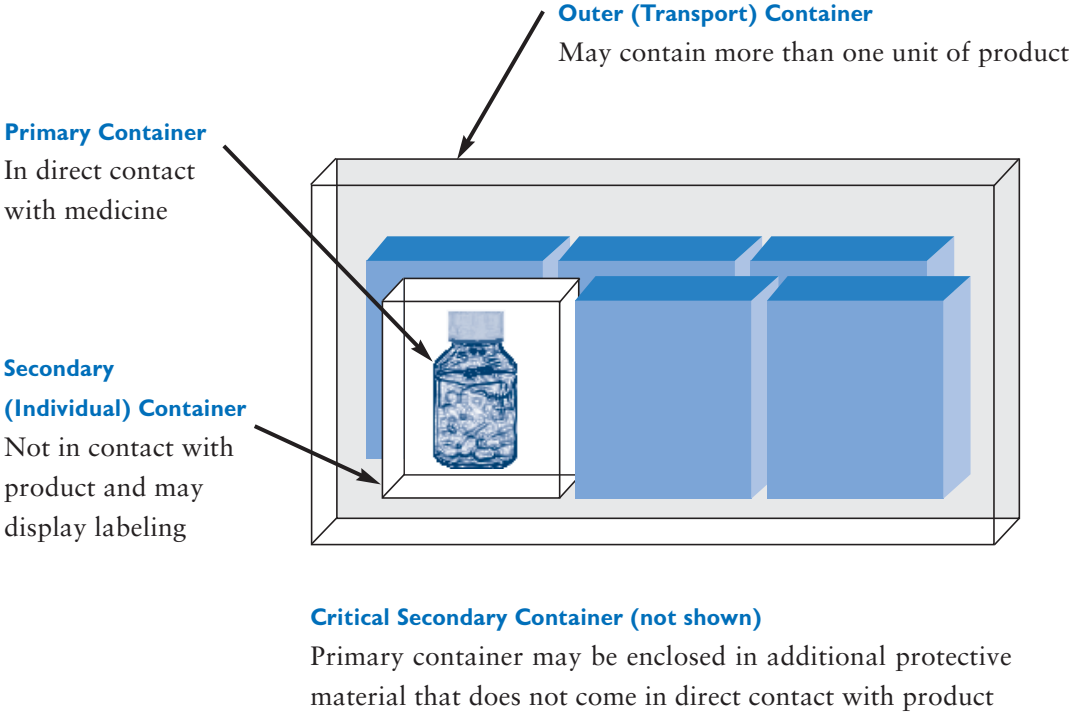
Packaging for medicines is generally divided into four types of containers, defined by their characteristics and uses.[3] ASTM International, one of the largest, most trusted voluntary standards development organizations in the world for technical standards for materials, products, systems, and services, defines the packaging[4] as:

- **Primary container**—comes in direct contact with the medicine and protects it from environmental hazards during storage and handling;
- **Critical secondary container**—not in direct contact with the medicine but provides essential product stability protection;
- **Secondary container**—encloses one or more primary containers and is usually designed for final market presentation to carry labeling; and,
- **Additional packaging**—a variety of packaging used to hold primary containers. (***United States Pharmacopeia 30–National Formulary 25, 2007b***)

Figure 6.3
Container system for shipping medicines

Inspect all shipping cartons and contents

(Adapted from USP, 2007a)



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

Additional product information. Literature that extensively describes the product—that is, literature from the product dossier and the patient package insert—including directions for use, contraindications, and so on, should be requested from the supplier. The national MRA establishes regulations concerning medicines information requirements. Final responsibility for the text, however, rests with the manufacturer.

Identify candidates and select qualified suppliers

The choice of supplier is closely tied to the procurement method. Four methods for procuring medicines include direct procurement, competitive negotiation, open bid, and limited bid.[5] Open bid, limited bid, and competitive negotiation require that several suppliers compete for the right to sell and deliver medicines which generates favorable pricing. Direct procurement, on the other hand, involves a single supplier and does not usually result in favorable pricing. This procurement method is used primarily for small-value and emergency purchases.

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 invitation to bid is released; thus, only prequalified suppli-

ers receive a request for bids. In postqualification, the evaluation process is conducted after the bids have been received.

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

PREQUALIFICATION

Prequalification focuses on the technical and financial capabilities of prospective suppliers, without reference to price or contractual conditions.[6] 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 establishes the list of suppliers that will receive the bidding documents. The prequalified supplier list must be updated periodically to add more suppliers, thus improving competition and lowering prices.[7]

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 other information exchange;
- Site inspection;
- Targeted laboratory testing;
- Informal local information-gathering;
- Using suppliers of prequalified medicines.

Product registration. Medicine manufacturers, suppliers, or their agents submit the product dossier and certifications required by the procuring MRA to officially register the product for distribution and use. The procurement office subsequently needs to request a copy of the supplier's registration certificate from the MRA to confirm that the product has been officially registered for use in the country of export.

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 medicine regulatory capacity to obtain partial assurance from exporting countries about the safety, quality, and efficacy of the medicines they plan to import. It provides an inexpensive way for a procurement office to gather product quality information; however, the effectiveness of the WHO Certification Scheme and the reliability of the certificates issued under it depend largely on the willingness, reliability, and capability of the participating medicines regulatory authorities.

When conducting supplier prequalification, the procurement office would request the certificates described below.

Certificate of a pharmaceutical product (product certificate). The WHO model certificate issued by an MRA in the exporting country, which confirms that a medicine is approved for use in the exporting country. If the product is not approved, the MRA explains the reasons why. 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 (see **Form B**).

Statement of licensing status. The WHO model statement of licensing status which confirms that a license has been issued for the product for use in the exporting country (see **Form C**) (World Health Organization, 1997a).

Batch certificate of a pharmaceutical product. A WHO model certificate requested by the purchaser in the bid documents. The batch certificate is a production record submitted by the manufacturer after production to confirm that individual batches conform to quality specifications. Though it is not requested in a prequalification exercise, it is an important document required in the bidding process (see **Form D**).

Supplier questionnaire. A questionnaire can be used to obtain data, such as that described below, about a supplier's business, manufacturing practices, and products. (See **Form E** for a sample questionnaire that can be used in prequalifying suppliers of pharmaceutical products).

Business information. 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 for sale in the country of origin; and the names of the commercial director, the general manager, the quality assurance manager, and samples of their signatures.

Manufacturing information. Number of medicines manufactured; a copy of GMP[8] and other types of certification, for example, International Organization for Standardization (ISO); manufacturing license; name of the company plant where products are manufactured or name of the contract manufacturer; and information about the production site, such as capacity and air and water treatment systems.

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

Product information. List of active pharmaceutical ingredients and their source of manufacture; master file of drug registration numbers and country of registration; trade name; dosage form; regulatory status in the country of origin; Certificates of Pharmaceutical Product according to the WHO Certification Scheme; finished product specifications; stability information; therapeutic equivalence for multisource (generic) products; and storage conditions.

Reference checks and information exchange. A procurement office may wish to contact MRAs in other countries or purchasing groups, such as the International Dispensary Association, to obtain information regarding product or supplier questions. Networks for information exchange between medicines regulatory authorities, such as the WHO International Conference of Drug Regulatory Authorities (ICDRA),[9] can also be contacted. ICDRA meets every two years to exchange information and strengthen collaboration.

Informal local information-gathering. Information gathered from local agencies and individuals who have had experience with a potential supplier can be helpful in evaluating prior supplier performance. Although obtaining this information is often the simplest and least time-consuming option, it must be evaluated carefully for objectivity.

Site inspection. Under ideal circumstances, a supplier's manufacturing facility would at least be inspected for GMP compliance; however, for an inspection to be effective, the investigator must be trained in GMP inspection procedures. This often presents a challenge in resource-limited settings because of a lack of qualified inspectors and funds. The GMP certificate provided by the supplier that was issued by the MRA of that country, as well as information on the manufacturer's license, must be thoroughly evaluated for authenticity and validity. A procurement office might also consider hiring a qualified independent consultant to perform a site inspection.

Targeted laboratory testing. For all new suppliers, the procurement office arranges a visual inspection of a sample product's packaging and labeling. Procurement officers must bear in mind 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: laboratory testing. Samples submitted for testing should be retained for later comparison with delivered products.

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. When options for laboratory testing are extremely limited, priority attention should be given to testing products or categories of products for which concerns exist, such as medicines with a high potential for stability problems or counterfeiting. Countries that do not have access to their own quality testing laboratories are encouraged to use WHO-prequalified laboratories for checking the quality of products, including those acquired through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).[10]

Using suppliers of prequalified medicines. For certain medicines and pharmaceuticals, international agencies conduct an independent prequalification process in accordance with internationally accepted qualification procedures. For example, WHO prequalifies some vaccines, which allows United Nations agencies such as UNICEF to procure those vaccines from the manufacturer. The WHO Medicines Policy and Standards Department conducts a prequalification scheme for manufacturers of medicines that treat HIV/AIDS, malaria, and tuberculosis.[11] Purchasers who want to buy directly from suppliers whose products have been included on a prequalification list should note that only the specific medicines (API, dosage form and strength, manufacturing site listed on the dossier) have been prequalified, not the manu-

facturer's or supplier's entire product line. Even if that manufacturer or supplier has other prequalified medicines listed, that does not imply that *all* of their products are of comparable quality. A product included on the prequalification list does not guarantee prequalified status forever: All medicines are requalified after three years, or earlier if needed, depending on results of WHO random quality control testing during the interim.[12]

COMPILE PREQUALIFICATION INFORMATION

The procurement office assembles the information described above and submits the data it has compiled to the supplier prequalification committee for review. This committee would best be composed of a diverse group of health care managers and technical personnel that includes quality assurance experts and pharmacists. The committee evaluates the information on the suppliers for the prequalified list.

Prepare and release bidding documents

Bidding documents are prepared after appropriate medicines have been selected, quantities have been decided, technical specifications have been developed, and suppliers have been prequalified.

Quality control testing requirements that will be performed on finished products for acceptance of consignments and the public pharmacopeial standards to be used as references would be detailed in the bid document, as would 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.

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

Invitation to bid. Describes the overall procurement process, describes the conditions for accepting bids, and explains when bids are due. Instructions to bidders are provided, describing how bidders are to submit documents, criteria against which they will be evaluated, award procedures, and whether or not bid or performance bonds will be required.

Technical specifications. Identify specific product and certification requirements.

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

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

Bidding documents are then combined into a bidding document package, which is forwarded to prequalified suppliers who are required to submit their bid within a specified time period.

Receive and evaluate bids

Next, bids from suppliers are submitted in sealed envelopes to the procurement office by the date stipulated in the bid book. Bids must be stored in a secure location until the scheduled time for opening. They are usually opened at a prearranged date and time in the presence of participating companies. Traditionally, a committee comprised of personnel with technical expertise to examine the product documentation and certification submitted by suppliers evaluates the bids according to a set of pre-established criteria.

In limited 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 the company's capacity to deliver the products in accordance with delivery requirements.

The postqualification process is similar to that of prequalification with one exception: There are usually more suppliers to screen. Because postqualification is often conducted via an open bid process, the additional suppliers must be evaluated within a limited window of time. That process can place a significant burden on a procurement office with limited capacity. Consequently, limited bidding, in conjunction with a prequalification process that uses a combination of methods discussed above, is often the preferred method for procuring medicine products.

Award contract

Once the winning bid has been selected, the successful bidder is officially notified that it will be awarded the contract and that it 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 commercial terms (INCOTERMS),[14] payment terms, and methods for resolving contract disputes. The contract identifies the responsibilities of both parties, as well as terms and conditions, and becomes a legally binding document between the purchaser and the seller. A contract restates technical specifications about the product and quality assurance requirements identified in the original bidding documents, as well as modifications agreed upon by both parties.

Inspect product before shipment (pre-shipment)

Inspection requirements are always included in the contract issued to the supplier. The procurement office must decide whether or not to conduct a pre-shipment inspection. Pre-shipment inspection can prevent unacceptable products from entering the market that would negatively impact health care programs; however, it may require additional lead time. If an MRA does not have the necessary resources to perform inspections, several independent international companies are available that specialize in pre-shipment inspections.

Receive and inspect products (post-shipment)

SHIPMENT INSPECTION

Even when a pre-shipment compliance inspection occurs, all shipments still must be inspected when they arrive in a country to ensure they were not damaged in transit. Receipt inspection occurs when the product first enters the country, and consists of:

- Review of all shipping documentation;
- Inspection of all shipping cartons for damage and the contents of any damaged shipping cartons; and,
- Tests of a random sample of the product.

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 6.1).

Three inspection methods can help assure product quality:

- Inspection of documentation and certifications;
- Visual inspection of the products, including labeling, dosage form, strength, and packaging; and,
- Laboratory testing of the product.

The level of inspection conducted depends on the previous experiences with the supplier. See Chapter 9 for more about all aspects of product inspection.

REVIEW DOCUMENTATION

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 qualified personnel to review the documentation to confirm that the supplier performed the required tests during product manufacture and that reported test results meet GMP standards.

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] (See Annex 6.1 for random sampling guidelines.) Visual inspection will indicate signs of product and package damage, and product 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. A comparison of the inspection results to the requirements identified in the contract forms the basis for the decision to accept or reject a lot. A common practice should be to outline inspection and sampling procedures, indicating what measures to take when the sample fails the set standards.

CONDUCT LABORATORY TESTING

Laboratory testing of pharmaceuticals can be time-consuming and expensive and is usually reserved for products that:

- Have the greatest potential for bioavailability or stability problems.

- Are from new or questionable suppliers.
- Have received complaints.
- Are produced by manufacturers that have not yet received GMP certification.

The tests to be performed depend on the product characteristics and reason for testing. 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 against those of the samples that were originally submitted for testing.

The procurement office usually arranges for samples to be randomly selected from the consignment and forwarded to a national reference laboratory or a chosen independent laboratory. The purchaser is expected to pay for laboratory testing to ensure objective results. 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.

Monitor supplier performance and product quality

Adding problem-reporting systems will enhance the safety of the public health. It allows supply chain personnel, health care workers, and consumers to report suspected or confirmed problems with specific products.

Reports of problems generated by a reporting system, along with the results of any actions taken or tests conducted, can be shared with the procurement office for use in evaluating suppliers in the future.

If a medicine or product is determined to be of defective quality, depending on the level of hazard involved (e.g., predictably dangerous to the public health), it may be recalled immediately; the manufacturer or supplier is responsible for recall costs. Consequences for a supplier that does not adequately respond to the request to replace the product should be addressed in the contract. (See Chapter 9 for more information on recalls.)

For monitoring a supplier's performance, the procurement office should develop a formal 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 repeatedly experiencing product or performance problems, the procurement office and its technical committees need to determine the appropriate consequence. Depending on contract conditions, options might include:

- 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.

Additional Procurement Options

The Ministry of Health, or another relevant agency, may choose to follow alternative options for securing medicines, such as hiring the services of a procurement agent, using international agents, or participating in pooled procurement.

Procurement agents

If the agency staff lacks the expert training needed for procurement systems, a government may wish to consider retaining the services of a procurement agent. Before selecting an independent procurement agent, the MRA needs to verify the agent's experience, expertise, and qualifications.[16]

Direct procurement from international agencies

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

Regional pooled procurement

Procuring large quantities of medicines can increase buying power by lowering prices and obtaining better services from the seller. National governments in a given region might consider pooling procurement services. 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.

Although they are difficult to organize and sustain, 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 best when all participants gain. Having the following points in common will increase the chances of success for participating countries:

- Similar population size and economic strength;
- Other formalized cooperative bodies already in place;
- Similar public health structures;
- Similar essential medicines lists; and,
- Reciprocal recognition of national MRA registration requirements.

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

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

3. *United States Pharmacopeia.* 2007. General Chapters <1136–1150>, USP 30, The National Formulary 25 (USP-NF). Rockville, Md.: The United States Pharmacopeial Convention. Available online: www.uspnf.com.

4. ASTM International, originally known as the American Society for Testing and Materials (ASTM), Committee D10 on packaging publishes terminology, practices, test methods, specifications, guides, and classifications for testing and evaluating packaging (see ASTM D99695, "Standard Terminology of Packaging and Distribution Environments"). Available online: www.astm.org.

5. 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. Donors may also have requirements for tendering that must 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 Prequalification Document: Procurement of Health Sector Goods" (April 2002).

6. 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).

7. The intention of the WHO Prequalification Scheme is to facilitate access to medicines that meet unified standards of quality, safety and efficacy. For more information about the list of WHO prequalified medicines, which is updated quarterly, visit http://mednet3.who.int/prequal/.

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

9. The International Conference of Drug Regulatory Authorities (ICDRA) provides drug regulatory authorities of WHO member states with a forum every two years to meet and discuss ways to strengthen collaboration. For more information, see www.who.int/medicines/.

10. For more information on WHO prequalified laboratories, see http://mednet3.who.int/prequal/.

11. For more information on the WHO prequalification scheme, visit: http://mednet3.who.int/prequal/. For information on the Global Drug Facility, see www.stoptb.org/gdf/.

12. For more information about list of WHO prequalified medicines, visit http://mednet3.who.int/prequal/. (See note 7.)

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. For more information, see www.wto.org.

14. International Commercial Terms (INCOTERMS), 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. INCOTERMS are used in conjunction with a sales agreement or other sales transaction methods; for example, FOB (Free On Board) and CIF (Cost, Insurance, and Freight). For additional information, see http://www.export911.com.

15. For guidance on conducting random sampling, see the "WHO guidelines for sampling of pharmaceuticals and related materials," WHO Technical Report Series, Annex 4, 929/2005.

16. References should be obtained and contacted to confirm that the procurement agent being considered has a reputable history of service and the necessary technical expertise to procure the medicines requested, and that the agent provides services at a reasonable cost. Available online: http://www.who.int/prequal/info_general/documents/TRS929/WHO_TRS_929_annex5FDCs.pdf.

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 technical officer with experience in good procurement practices and international bidding procedures
  - ▫ One pharmacist
  - ▫ Access to legal counsel for contract support
- ☐ 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.
- ☐ When product testing is required, arrange to contract testing services with a qualified quality control laboratory.
- ☐ 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.

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 countries in need, 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 mutually beneficial outcome, where 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 medicines appears at the end of the chapter (**Checklist 7.1**).

Guidelines for Donations of Medicines

In 1996, the World Health Organization and several donor organizations developed ***Guidelines for Drug Donations*** (http://whqlibdoc.who.int/hq/1999/WHO_EDM_PAR_99.4.pdf), designed to improve—not discourage—the quality of medicine donations. The *Guidelines* describe good donation practices and may be used as a basis for a medicine donations policy.

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

- Offer maximum benefit to the recipient.

- Respect the wishes and authority of the recipient.
- Meet the same high standards of quality as the donating country.
- Result from effective communication between the donor and the recipient.

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

Ensuring the Quality of Donated Medicines

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

National Guidelines on Donations of Medicines

Section IV of the *Guidelines for Drug Donations* discusses medicines donation management and offers a list of important issues to address in national guidelines. The following paragraphs briefly explain those issues.

Define and prioritize medicine needs. Specify medicine needs according to the needs of a country's national health policy rather than based on quantities and medicine formulations proposed by donors. Further criteria for accepting donations can be found in the *Guidelines*.

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

Describe and develop official documentation required for medicine donations. Develop text for national guidelines for medicine donations and ensure that the guidelines are adopted by the relevant authorities. Disseminate guidelines among all concerned departments, including the Ministry of Finance, customs, port and airport authorities, government clearing agents, etc. Donated medicines should be exempted from port-of-entry excise tax and other duties.

Describe the registration requirements. Describe whether donated medicines should be registered with the MRA, exempt from registration, or follow a fast-track registration process. (Fast-track registration is discussed in Chapter 4.)

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, which should follow those the MRA requires for good-quality medicines 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 consideration 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 medicines might be higher, on a unit basis. Donations may also complicate pricing issues, particularly for revolving drug funds.

A national pharmaceutical industry that can produce good-quality products at competitive prices is an asset and ensures competition in the international medicines industry. When accepting donations, special care should be taken not to jeopardize the interests of the national pharmaceutical industry. Medicine registration policies, import levies and duties, protection of patent rights, and the Trade-Related Aspects of Intellectual Property Rights (TRIPS)[1] 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 waives the usual MRA registration procedures for pharmaceutical products being donated. This practice makes it possible for such medicines entering the country not to be subjected to the national guidelines for medicine donations. In this case, however, a fast-track registration process could be useful, allowing the full registration to take place after medicines have been received.

Countries who receive donated medicines should check what medicines and medical supplies have been sent and verify all documentation, particularly certificates of analysis. Donors, even though responding to emergency conditions, should communicate with recipients to learn what medicines are needed before sending any medicines.

Global Initiatives

Global initiatives—such as, the **Global TB Drug Facility** (GDF; http://www.stoptb.org/GDF/) and the **Global Fund to Fight AIDS, Tuberculosis and Malaria** (The Global Fund; www.theglobalfund.org)—have been created to accelerate the fight against AIDS, tuberculosis, and malaria.

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 WHO Directly Observed Treatment Short-Course (DOTS) strategy, either in the form of grants or for direct procurement 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 these donations should be exempt.

If there is no policy in place, requesting an emergency medicine donation could trigger the preparation and adoption of a national medicines donation policy by the MRA and other national stakeholders. Assistance in preparing requests can be sought from organizations such as **Management Sciences for Health** (http://www.msh.org), **Population Services International** (http://www.psi.org), **U.S. Pharmacopeia Drug Quality and Information Program** (http://www.uspdqi.org), or John Snow, Inc. (http://www.jsi.com). General information on medicines donations can also be obtained from **The Partnership for Quality Medical Donations** (PQMD; http://www.pqmd.org).

1. For more information, see http://www.wto.org.

Checklist 7.1
Effective donations of medicines

- ☐ Develop national guidelines for accepting donations of medicines.
- ☐ Ensure national guidelines are adopted by all authorities concerned before donations are requested or needed.
- ☐ Ensure that national guidelines for medicines donations are in line with all national provisions regarding medicines regulations, especially those governing medicines registration.
- ☐ Specify procedures for handling medicines 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 medicines donations.

CHAPTER 8

Laboratory Testing and the Three-Level Approach to Testing

The quality of medicines is a topic of 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 resource-limited countries. Some countries are addressing this problem by developing a medicines policy that has a country-specific quality control system. A national medicines quality control laboratory (QCL) should be able to assess the quality of all essential medicines used in national health programs, including those manufactured locally, imported, or donated.

One way to assess the quality of a medicine is to test it, but many countries do not have a QCL 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 proliferation of counterfeit and substandard medicines has been exacerbated by the absence of functional QCLs in much of the developing world.

Ideally, a country's medicines regulatory authority (MRA) conducts product pre-approval 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 are responsible for testing products prior to distribution.

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

Medicines Quality Control Laboratory

The World Health Organization (WHO) has encouraged its member states to maintain a QCL or, if a member does not have its own, to use a WHO collaborating QCL (World Health Organization, 2002a). The WHO has also published detailed guidelines for good practices for national pharmaceutical control laboratories (World Health Organization, 2002b).

Governments, usually through an MRA, establish and maintain a QCL 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 QCL.

To ensure patient safety, the role of a quality control laboratory must be defined in a nation's general medicines 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 medicines quality must be based on data supplied by manufacturers or importers.

Laboratory testing

QCLs test medicines according to specific monographs in officially accepted national or international pharmacopeias. A monograph determines which test methods to use and the appropriate standards, specifications of tests, references for analytical procedures, and test acceptance criteria for each specific medicine. In general, a monograph for a solid dosage form includes acceptable 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 for excipients are generally not performed in pharmaceutical dosage forms.

If no monograph exists for a particular medicine, a QCL 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 medicines legislation, MRAs will commonly accept the manufacturer's label statement and release test methods as the standard. 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.

A QCL, depending on its capacity, needs to be capable of performing several tests—identity, assay, disintegration, dissolution, bioavailability, bioequivalence, impurity, sterility, and stability tests—to assess the quality of medicinal products.

Figure 8.1
Key laboratory tests to evaluate medicines quality

Minimal tests required to evaluate medicines product quality. To conserve resources, a sample must pass one test before moving on to the next.

1. **Identity—verifies identity of API**
2. **Assay—determines API content**
3. **Disintegration—determines that solid dosage form will disintegrate**
4. **Dissolution—demonstrates that medicine will dissolve in the body**

IDENTITY TEST

A pharmaceutical identity test should be considered one of the most important tests for checking the quality of a pharmaceutical product; if a medicine fails the identity test, there is no need to test any further. According to the WHO, 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 active pharmaceutical ingredient(s), bulk starting materials, 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

An assay test is considered to be the second-most important test for quality control because it determines the API content after it has been identified. Thus, the content of APIs must be determined by an assay test.

There are different methods and procedures used for assay tests, determined by the individual pharmacopeial monograph. The most commonly used methods are titration, spectrophotometry, and chromatography.

DISINTEGRATION TEST

This test determines whether a pharmaceutical solid dosage form (tablet or capsule) will disintegrate within the specified time when placed in a liquid medium at the temperature of 37°±2°c (between 35° and 39°c). Except where the label states that the tablets or capsules are intended for use as troches, are to be chewed, or are designed as extended- or delayed-release dosage forms, the disintegration must comply with the limits stated in the individual monographs.

In the field, where basic testing is used, disintegration can be performed using tap or distilled water in a 100–150 mL wide-neck bottle. In a laboratory setting, the apparatus used might be a basket-rack assembly with a specific 1000 mL low-form beaker and thermostatic arrangement for heating the fluid, or it might be disks.

DISSOLUTION TEST

The next important step tests a medicine for dissolution; if a medicine fails the dissolution test, there is no need to test any further. In the dissolution process, a solid substance changes into a solvent yielding a solution. Dissolution can serve as a quality control test by providing evidence of the product's physical consistency and manufacturing process. It is a critical regulatory and compendial requirement in the testing of solid dosage forms and quantitatively determines the *in vitro* biological availability. Thus, if an *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.

STABILITY TEST

This test obtains information on the stability of a pharmaceutical product; that is, the medicine's ability to retain its chemical, physical, microbiological, and biopharmaceutical properties over time. The product's stablility will determine its shelf-life (the date from its manufacture to its expiration) and utilization time period under specified packaging and storage conditions. The stability of a medicine depends on many factors:

- Environmental (ambient temperature, humidity, and light).
- Product-related (chemical and physical properties of active ingredient(s), excipients, manufacturing process, container-closure system, and packaging materials).

The manufacturer is responsible for carrying out the stability tests for each of the medicines it produces.

There are two types of stability tests: accelerated and real-time. Depending on its objectives, the stability test would be designed and carried out according to the type of studies. The table below describes the aims, types, and purposes of the test (WHO, 1997a).

Figure 8.2
Stability test objectives

OBJECTIVE	TYPE OF STUDY	USE
Select adequate formulations and container-closure systems	Accelerated	Development of the product
Determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
Substantiate the claimed shelf-life	Real-time	Registration dossier
Verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control

A stability study should be designed to take into account the intended market and climatic conditions. For example, the accelerated study for a product to be sold in Zone IV climatic conditions (hot/humid) would be carried out at 42°±2°c with relative humidity of 75±5% and a six-month study duration (WHO, 1996a).

STERILITY TEST

Sterility is a critical property for all parenteral drug products and is required to ensure patient safety. If a monograph requires a sterility test, then no microorganism 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 only under sterile conditions by well-trained analysts.

IMPURITY TEST

Impurities are foreign contaminants present in a finished dosage form. Tests to identify and quantify impurities cannot be routinely performed by most QCLs in resource-limited countries due to the high technological requirements and expense.

BIOAVAILABILITY/BIOEQUIVALENCE TESTS

The quality of a pharmaceutical and its behavior in the human body is assessed 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. Bioequivalence indicates that a drug in two or more dosage forms reaches the general circulation at a similar relative extent. For more information on BA/BE issues, see Chapter 12.

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.

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).

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 QCL 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 QCLs might participate in these reviews. This capacity is often available through pharmacy school faculty.

Cost of laboratory testing

The high price of reagents, equipment, and reference substances can make laboratory testing very costly. When orders are more frequent and the size of the order is small, pooling samples among recipients can decrease costs. Some countries have established cost-recovery schemes in which testing fees are charged to applicants or registrants during product registration; however, laboratory testing related to pre-shipment and postmarketing is usually paid for by the purchasing government. Testing fees could be included in registration charges, but the test could be performed on samples obtained from post-approval or postmarketing surveillance. Test results should be compared with those from samples initially 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 MRAs. 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 sampling on products at high risk for counterfeiting. General guidelines for sampling pharmaceutical products can be found in the WHO sampling procedure for industrially manufactured pharmaceuticals (**World Health Organization, 2005**).

Medicine products to be sample-tested are also selected according to a risk-based strategy by targeting those products with the greatest potential to harm the public health. For example, these products 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. (See CD-ROM for **USP DQI Model Sampling Guidelines.**)

Sampling criteria for quality control

Sampling should be performed by the MRA or its appointed representative. 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.

The Three-Level Approach to Testing

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 medicines quality control (Figure 8.3).

Level 1—Screening tests

External quality checks should be performed on every consignment. Visually inspecting the integrity of packaging, appearance of tablets, or other dosing forms may help identify potentially substandard products. An examination of remaining shelf-life and 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 manufacturing, such as crumbling, chips, or cracks in solid dosage forms.

Visual and physical inspection of pharmaceutical products is the first step in any quality control program. Visual inspection helps ensure 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.

VISUAL INSPECTION OF 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. Negative 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,

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)

Figure 8.3
Three-level testing approach in relation to location and purposes

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 required, the compatibility with the contents, the filling method, user cost, presentation (in the case of over-the-counter medicines), 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 medicine and its packaging. During visual inspection, inspectors should verify that the package is appropriate for the medicine contained within and ensure that the package protects the medicine as indicated by the storage conditions. (See Storage and Distribution, Chapter 9.)

VISUAL INSPECTION OF LABELS

All finished medicinal 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;
- Registration number, if applicable.

Level 2—Basic testing

The minimum tests recommended for basic testing are the identity test and approximate content. For oral solid dosage forms, a simplified disintegration test can be conducted. Some countries already use thin-layer chromatography as an identification test, and a disintegration test for oral solid forms. Studies have proven that this level of testing could mean that a QCL will test fewer samples. The basic tests for medicines to treat malaria and tuberculosis have been accepted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

A variety of chemical reagents, plates, equipment, and drug reference standards are required to perform TLC. Ready-to-use TLC kits are available through the German Pharma Health Fund (http://www.gphf.org. GPHF-Minilab® kits—portable, easy-to-use, self-contained laboratories—contain the essential labware and chemicals, as well as authentic tablets and capsules for reference purposes, to test some 40 essential medicines. The GPHF-Minilab® has been developed for rapid drug quality verification and counterfeit medicines detection only. (Other organizations may offer similar kits.)

Basic tests cannot replace extensive testing on questions of drug release, chemical purity, or microbial burden; those and detailed forensic testing for court actions must be referred to a comprehensive drug quality control laboratory that employs legally accepted methods. The U.S. Pharmacopeia Drug Quality and Information Program, in conjunction with GPHF, has developed training materials for the basic tests that can be performed using the Minilab®; they are included with the Minilab®. For more information, visit the GPHF website.

COLORIMETRIC TESTING METHODS

Colorimetric tests are generally used for identifying an API in solution form. A colorimetric test shows the chemical reaction between the active pharmaceutical ingredient in a medicine and the analytical reagent(s), with or without an indicator solution. This chemical reaction is used to transform a normally colorless chemical compound into colored derivative(s) which can be detected visually or with the aid of an instrument. Because the perception of color is both subjective and objective, the result depends on three variables: Spectral properties of the object, spectral properties of the source of illumination, and visual discernment of the observer. The colorimetric test should be carried out by an experienced analyst in a laboratory setting.

DISINTEGRATION

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

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.

Medicines obtained from unusually cheap sources, products with missing or incorrect documentation, products with defective dosage forms or packaging, and products with labels that are incomplete, damaged, missing, or written in a foreign language should be subjected to an identity test.

Level 3—Complete testing

Level-three testing is performed only for products deemed questionable through physical observation, laboratory testing, suspicious adverse reactions, or those that may provide potential evidence in litigation issues. Products that are considered counterfeit should also be tested.

If a country does not have the resources to perform complete pharmacopeial testing, other options exist; for instance, using a WHO collaborating laboratory or contracting with a certified, accredited private laboratory.[1]

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

Figure 8.4
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 ■ 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.	All the equipment in the first category is needed, plus the following: ■ Mass spectrophotometer

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.

Third-level testing aims to:

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

More comprehensive tests may need to be performed for products with the following concerns:

- Physical signs of instability or deterioration;
- Unidentifiable origin;
- Sold by a supplier suspected of dealing in substandard products;
- Disputed analytical results;
- Suspected of causing adverse reactions;
- May be used as evidence in litigation;
- Provided through medicine donations;
- Suspected of containing certain impurities not mentioned in compendia specifications; and,
- Does not contain the labeled active pharmaceutical ingredient(s).

The importance of establishing a QC laboratory

Countries are strongly encouraged to establish at least one Category 1 QC laboratory of their own for a number of reasons. More important even than the time and expense saved by testing medicines locally, the presence of a national QCL may deter those who manufacture, import, or sell counterfeit or poor-quality medicines. Visual inspection of all medicines consignments and confirmation of at least their identity and content must occur to assure the quality of essential medicines. Whether or not it has an QC lab, a country is responsible for ensuring the safety, efficacy, and quality of medicines.

Other options exist for conducting medicine testing:

- University laboratories, research laboratories, WHO collaborating laboratories;[2]
- Regionally qualified medicine quality control laboratories; and,
- Private laboratories.

1. WHO Collaborating Centers Related to Pharmaceuticals and Medicines; www.who.int/whocc/.
2. Ibid.

CHAPTER 9

Maintaining the Quality of Medicines Through Storage and Distribution

Good medicine quality depends in part on proper storage and distribution practices. Using methods that protect product integrity from handling and changes in temperature are needed throughout the distribution chain in order to maintain the quality and stability of medicines.

Guidelines for maintaining the quality of medicines through good storage practices can be adapted from the World Health Organization's *International Pharmacopoeia* (2003d), the *United States Pharmacopeia* (2007c), and other pharmacopeia. Any guidelines should complement, rather than replace, a nation's existing processes and procedures.

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

Policy and Legal Framework

Everyone involved in handling and distributing medicines should be familiar with the national and regional policies related to medicines. National medicines policies should identify the roles played by pharmaceutical manufacturers, importers, wholesalers, retailers, pharmacists, and other health care professionals in complying with regulations that govern:

- Production and importation;
- Warehousing and distribution;
- Prescription medicines;
- Over-the-counter medicines;

- Dangerous and controlled substances (narcotics, psychotropic medicines, etc.);
- Quality control and quality assurance of registration, licensing, inspection, monitoring, and evaluation; and,
- Personnel training in personal hygiene, sanitation, and proper use of protective clothing.

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

Figure 9.1
Minimum quality assurance/quality control 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.

Storage

Good storage practices involve more than maintaining adequate facilities. It is equally important to develop procedures for receiving, labeling, inventory, and security.

Key points of good storage practices

- Limit access to storage areas to authorized personnel.
- Ensure proper storage conditions (temperature, humidity, lighting).
- Organize and clearly label storage areas.
- Label clearly an expiry date on all containers.
- Arrange products following First Expiry/First Out (FEFO) and First In/First Out (FIFO) principles.
- Perform regular inventories of pharmaceutical materials and products.
- Maintain records of all materials in storage and update regularly.

Safety and security

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.

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 need to have clearly marked fire exits, and all personnel should be familiar with those locations. Smoke detectors should be checked 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, the amount of space required, transport accessibility and convenience, and security need to be factored in. 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 shelves, clearly labeled, and there must be easy access to products stored on top shelves.

Storage areas must be well organized and easily accessible, with separate areas for storing different categories of materials and products—packaging materials; raw, intermediate, and finished products; products in quarantine; and released, rejected, returned, or recalled products.

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, which tend to create airborne dust; a dust mop is preferable;
- After dusting, mop with soapy water or disinfectant; and,
- Avoid direct contact between cleaning solution and storage containers.

Storage conditions

Storage conditions should be monitored for temperature weekly or, if possible, daily, and records should be kept. Equipment used for monitoring storage conditions—thermometer and hygrometer—should be calibrated at defined intervals, according to standard operating procedures (SOP).

All necessary precautions should be taken to minimize conditions adversely affecting 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. If humidity can be controlled, products may be stored up to 30°C. Extraneous odors, other indications of contamination, and intense light must be excluded.

Storage Label	Recommended Storage Condition
Store between 15°C and 25°C	Store at normal room temperature
Store between 2°C and 8°C	Refrigerate; do not freeze
Store between 8°C and 15°C	Store in a cool place
Store below 8°C	Refrigerate
Store between -5°C and -20°C	Freeze
Store below -20°C	Deep freeze
Protect from moisture	No more than 60% relative humidity in normal storage conditions; to be provided to the patient in a moisture-resistant container
Protect from light	To be stored and provided to the patient in a light-resistant container

Source: Adapted from World Health Organization, 1996a, and United States Pharmacopeia, 2006. *Good Storage and Shipping Practices,* USP 29, The National Formulary 24 (USP–NF). Rockville, Md., The United States Pharmacopeia.

Figure 9.2 Recommended storage conditions according to specific labels

Medicines require appropriate storage instructions. Unless specifically stated, temperature deviation may be tolerated only for a short time, such as during local transport. Figure 9.2 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. Use of commercially available refrigerators designed for medicine products is recommended instead. Temperature can be monitored with a thermometer that has an accuracy rate of ± 0.5°C.

Here are two general storage rules to follow (also see Figure 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, including the handling of expired materials or products, should be well maintained and easily accessible. These should adequately describe the storage procedures and the distribution history 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, including a description of the products, their quality as described on the label, quantity, name of supplier, supplier batch number, date of receipt, assigned batch number, and expiry date should be kept. 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 data sheets (MSDS), which can be obtained from most medicine manufacturers, should be displayed and clearly visible in storage areas.

Labeling and containers

Proper containers should be used to store all pharmaceutical products to avoid contamination. All finished medicine products should bear labels that include their 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; and,
- Reference to the pharmacopeia, where applicable.

Inventory

An inventory software program is the most efficient method for controlling inventory management;[1] however, a monthly inventory check can be performed by hand using a simple checklist to compare actual product to product records. 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 stored in 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. Expired or rejected products should be identified and controlled under a quarantine system; the control of these products is then turned over to the medicines regulatory authority (MRA).

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 re-evaluation.

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 must be maintained for all receipts and issues of materials, according to a specified system (e.g., by batch number). Taking the following steps at the time of receipt will contribute to maintaining controls:

- Goods should match the appropriate 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 follows the 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 medicines, 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 (see "Key points" below).

Clearing medicines swiftly through customs at the port of entry is critical to preventing deterioration of their quality, especially in countries classified as climatic zone IV territories with very high temperature and humidity. Some measures described in "Key points" could help prevent problems from arising.

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 influences 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, address, facsimile, and telephone numbers, and email address, if applicable; product description, including name, dosage form and strength, batch number, and quantity; and transportation and storage conditions. The wholesaler or importer could provide a certificate of analysis for each product it distributes, which would indicate that the medicines passed quality standards testing before its distribution.

Key points of distribution practices

- Clear products rapidly through customs to avoid storage condition deterioration and fees.
- Inspect medicines 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 medicines arrive.
- Clearly label containers.
- Maintain delivery records.
- Provide easy access to delivery records.

Medicine consignments can be cleared more quickly through customs by following these procedures:

1. Designate an experienced staff person in port clearance to be responsible for custom clearance activities and processes.
2. Establish a written protocol for customs clearance and make sure it is followed.
3. Communicate frequently with the supplier/consigner to provide all necessary documents as required by the national and local regulations on custom clearance as soon as they are available. These include, but are not limited to, packing lists, airway bills, and pro-forma invoices.
4. Communicate frequently with the supplier/consigner and the port authorities (customs) enquiring about the status of the shipment, e.g., expected arrival dates and time, mode of transport, etc.
5. Collect and prepare all required documents with necessary signatures and stamps before physically going to the port.
6. Coordinate with all relevant authorities and with the customs officer, making an appointment in advance, if applicable, to inspect the shipment.
7. Make every effort to ensure that the customs clearance takes less than two (2) weeks.

Figure 9.3
Measures to take for rapid customs clearance of medicines consignments

Transport

The mode and duration of transportation, as well as the destination, must be taken into account to ensure the integrity of the medicines in transit. The two primary factors to consider concern 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.

Small-volume deliveries that require a short transit time (less than three hours) can be adequately protected by insulated packaging, without cooling elements. Larger deliveries requiring longer transit time should be transported in proper cooling environments. When using dry ice (solid CO_2), measures must be 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

The manufacturers and distributors—importers and wholesalers—are responsible for the recall of defective products from the market. They should have a written plan in place for product recalls that can be put into effect if needed. The person responsible for implementing the recall process should have the plan available; the plan should include handling the report,

notifying the relevant parties (e.g., the MRA and supplier) of the incident(s), and carrying out the recall and documentation.

The recall might be voluntary or, depending on the level of hazard involved, it could be mandated by the MRA. Within the product recall program, a formal reporting system—ideally using preprinted, simple reporting forms—should be established throughout the supply system that encourages personnel to report potential problems of poor product quality. At every level—retail, distribution, and manufacture—it should be clear to whom the report of a perceived quality problem should be made. All reports should be carefully assessed to establish the need for further laboratory testing and appropriate follow-up action including product recall, if warranted. Product defect reports and results should be recorded as part of the supplier monitoring system in both supplier and distributor product files.

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 should be required to replace defective products at its own expense. The purchaser may consider withholding payment until defective products are replaced. Replacement and payment options should be built into the contract.

---

1. 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 characteristics:
  - ▫ Adequate lighting and ventilation;
  - ▫ Smooth and clean walls and floors;
  - ▫ Floor in good condition, with no stagnant water;
  - ▫ Dry, well-ventilated storage premises;
  - ▫ 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 support;
  - ▫ 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 Figure 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 medicines match 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 regulatory requirements; records should be easily retrievable.
- ☐ 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 that delivery time is kept to a minimum.
- ☐ Do not delay port clearance for more than one week.
- ☐ Provide direct access to an international telephone line for managers of warehouse, import department, and quality assurance/quality control personnel.

STORAGE AND DISTRIBUTION

- ☐ Keep medicine 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.
- ☐ 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 the Quality of Medicines at the Dispensing Level

The last step in the process of providing high-quality medicines to patients requires rational prescribing practices, good dispensing procedures, and patient adherence. This chapter provides people who dispense medications with guidance on preserving and monitoring the quality of medicines. It identifies specific actions they can take to ensure that appropriate medicines of good quality are properly dispensed and used. Inappropriate prescribing and dispensing practices can jeopardize the quality of patient care and negatively affect treatment.

Some of the text for this chapter, particularly the practical steps to be implemented, has been adapted from the Management Sciences for Health book, *Managing Drug Supply* (1997; pp. 484–489). Additional information can also be found in *Good Pharmacy Practice* (International Federation of Pharmacists, 1997), *Good Pharmacy Practice In Developing Countries* (International Federation of Pharmacists, 1998), and *Good Pharmacy Practice in Community and Hospital Pharmacy Settings* (World Health Organization, 1996c).

Role and Responsibilities of Dispensers

Dispensing is often considered to be simple and routine, with little room for error. However, the significant investment made in ensuring product quality up to the point of dispensing may be lost if the correct medicine 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.

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

1. Maintaining a proper dispensing environment;
2. Receiving and checking medicine/supply orders;

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.

Maintaining a proper dispensing environment

Keeping a clean, organized environment can reduce the chance of making dispensing errors, protecting both dispensers and the public from hazardous situations. To maintain the highest standards possible during the preparation process, the work setting should exhibit the characteristics described below (Winfield, et al., 2003).

Building layout. The building housing the medicines outlet should be a spacious, permanent structure, with an efficient working area that allows staff to move freely.

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

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

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

Staff hygiene. Dispensing personnel must practice good personal hygiene, according to standard operating procedures (SOP), to avoid product contamination.

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

Inventory rotation system. Using an inventory rotation system, such as First Expiry/First Out (FEFO) and First In/First Out (FIFO), avoids product loss from expiry and ensures that medicines are monitored regularly and that quality is maintained at all times.

Proper record maintenance. Accurate and up-to-date records must be retained for all products issued in compliance with national and local regulations. For hospital dispensers, a list of available medicines should be updated at each location so that prescribers know which medicines can be used; local dispensers should follow their SOP for inventory.

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

Proper storage conditions. Products should be stored as much as possible according to the storage conditions recommended by the manufacturer—temperature range, light exposure restrictions, closed containers, etc.—to maintain product quality.

Receiving and checking medicines orders

When medicines arrive at the dispensary, staff are responsible for making sure that the product conforms to what 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. The package should be visually inspected for damage and proper sealing.

The product should be visually inspected for discoloration, deterioration, and physical degradation.

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 and defective products should be returned to the supplier as stated in the agreement; if return is not feasible, they should be disposed of according to SOPs or local regulations.

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 name of the medicine prescribed and the patient's name, age, and address.
- Interpret any abbreviations written by the prescriber, and contact the prescriber, hospital, or medicines information center (MIC) with questions.
- 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 any questionable possibilities.

Preparing medicines for dispensing

Proper medicine preparation practices must be followed when dispensing medicines. Following a regular routine when dispensing helps make sure that medicines are handled correctly and reduces the possibility of medication errors or other mistakes. Developing a written policy and standard operating procedures provides a clear direction to pharmacy staff as to what is expected. Standard practices for the preparation of medicines are outlined below:

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 be done on a clean, dust-free surface. Options for counting include using a triangular tablet counter, a sheet of paper and a knife, or pan weighing scales. To avoid product contamination, a dispenser's hands should never directly contact the product. 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, because 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 non-pharmaceutical preparations, such as food and drinks.

Label the product. The label should include information about the brand and generic international nonproprietary names, strength and dose, frequency and duration of use, dispensing and expiry dates, patient name, supplier name and address, and child safety and other warnings.

Double-check the preparation against prescription and storage container. A second dispensing staff member should double-check the preparation against both the prescription and its storage container before releasing it to the patient (**Management Sciences for Health,** 1997, p. 489).

Recording the actions taken

In order to track inventory, records must be maintained of all products dispensed. This allows contact with a patient should a problem with the medication arise. 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 prescriber and the dispenser.

Issuing medicines with clear instructions and advice

To enable patients to comply with the instructions on the prescription package, they must be clearly written. The container should list what the medicine is used for; what the dosage is; when to take the medicine and for how long; how to take the medicine; and how to store and care for the medicine (i.e., use-by date or end of treatment) (**Management Sciences for Health,** 1997, p. 489).

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

Requirements in Basic Dispensing Functions

Appropriate training

Medicines 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; and,
- Ability to communicate effectively with patients (Management Sciences for Health, 1997, 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 medicines usage. For details on storage of medicines, see Chapter 9, Maintaining the Quality of Medicines Through Storage and Distribution.

Strengthening good dispensing practices

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

- Encouraging professional organizations to promote the use of good dispensing practices guidelines, such as the *Good Pharmacy Practice in Developing Countries* from the International Pharmaceutical Federation (1998b), will elevate the importance of adhering to them.
- Empowering 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 help ensure good dispensing practices.
- Providing adequate and appropriate dispensing materials, such as dispensing trays, medicine envelopes, dispensing cups, spoons, bottles, and jars will make dispensing medicine easier and more practical, minimize mistakes, and instill confidence and pride.
- Establishing a reward system to be given to the best dispensing outlet will encourage all dispensers to follow good pharmacy practices.

Checklist 10.1

Managing the quality of medicines at the dispensing level

DISPENSING PREMISES

- ☐ Approved by the appropriate regulatory authority.
  - ▫ Adequate lighting and ventilation in premises.
  - ▫ Adequate security installed to prevent break-in and theft.
  - ▫ Walls and floors smooth and clean.
  - ▫ Floors dry and in good condition.
  - ▫ Dry, well-ventilated storage room
  - ▫ Premises have adequate lavatory facilities, including running water and a hand drier to promote personal safety and hygiene.
  - ▫ Premises conducive to effective communication and ensure sufficient privacy between the dispenser and the patient.

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

- ☐ Pharmacist manages the medicine dispensary; a pharmacy technician or other trained personnel assist under supervision of the pharmacist.
- ☐ 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 a reward system.

OPERATION

- ☐ Ensure the presence of at least one pharmacy technician or one trained staff member in the dispensary at all times.
- ☐ Enforce adequate standard operating procedures to enable staff to perform their work.
- ☐ Confirm that the correct medicines are dispensed (against the prescription or order) in the right dosage form, strength, quantity, packaging, and labeling to the right patient for the right indication.
- ☐ 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 Expiry/First Out (FEFO) and First In/First Out (FIFO) principles and practices.
- ☐ Evaluate whether patients understand how to take the medicines they have been prescribed.

STORAGE

- ☐ Keep medicine 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 unto itself is no more than an active pharmaceutical ingredient and excipients formulated to treat, prevent, or alleviate symptoms of illness or disease. The information provided with that medicine—directing a health care worker how to prescribe it or a patient how to use it—merits equal importance. The misuse or irrational use of medications in many countries—often due to the lack of an unbiased source of information for medicines 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 to 60 percent of primary health care patients receive antibiotics, perhaps twice the rate than is clinically necessary. A technical review by the United States Pharmacopeia of antimicrobial medicines information in six countries found that information on proper indications, dosage, precautions, and side effects was typically lacking at a variety of levels (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 medicines 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 medicines 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 policies for medicines. 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.

A sound system for adverse drug reactions monitoring is also needed. 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 medicine 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 those limits that must 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. A commitment to public health at the national level is essential.

Medicines Information Centers and Networks

A medicines information center[1] (MIC) provides objective, accurate, and up-to-date information about medicines and their use. MICs can communicate a better understanding of medicines to health care workers 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.

The objectives of a medicines information center could include one or many of the following functions depending upon the needs of the community it serves:

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

Standard of good-quality medicine information

The standards for a chemical or active pharmaceutical ingredient have been well understood and well supported for many years. Familiar guidelines such as those covering Good Manufacturing Practices are the mainstays of the manufacturing process.

Information about medicines also needs to be held to high standards; medicine information should be objective, independent, scientifically validated, evidence-based, and up-to-date.

Establishing a medicines information center

Although medicines information centers may be housed in a variety of facilities, their location is closely related to their immediate objectives and their target populations (see Form F). Many medicines information centers are established in teaching hospitals; such a location generally offers certain advantages:

- Facilitates the development of responsive information activities, a fundamental objective of any MIC.
- Encourages direct interaction with health professionals, primarily medicine prescribers.
- Provides better access to high-risk groups that could benefit from patient educational programs.
- Provides a better opportunity for immediate solutions to medicine-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 medicine control programs, and (2) to advise policy decision-makers.

Medicines information centers can also be established in allied health schools, or more typically, in schools of pharmacy. 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 settings for MICs whose objectives are to update prescribers and dispensers in the rational use of medicines and educate consumers.

Besides needing a room for providing information about medicines, MICs require at least two dedicated, appropriately trained staff members—physicians, pharmacists, or clinical pharmacologists—to answer queries. The staff will need the support of information technology personnel and the appropriate resources for answering queries received by the unit (see Figure 11.1). The MIC must document the queries received and answers provided.

An MIC needs an office with access to the following:

- Photocopier
- Computer
- Fax machine
- Internet
- Telephone
- Printer
- Answering machine
- Resource library

Figure 11.1
MIC equipment requirements

Figure 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 medicine reaction reports per year

Having the support of volunteer experts, perhaps in the form of an advisory board or editorial board for a medicines information bulletin, can also contribute to the success of the MIC. Having experts volunteer their time at the center, one person per day on a rotating basis, supplements the available staff to draw upon and broadens the base of knowledge for answering inquiries. Some MICs also allow medical and pharmacy students the opportunity to train at the center on literature evaluation and medicines information skills, providing them with hands-on training and the center with future staffing.

Medicines information centers must actively promote their services. This is particularly important when the service starts, as many practitioners and members of the public will find an MIC a new concept. For instance, an inauguration ceremony could be held, announced by a promotional campaign of flyers and invitations to clinics, hospitals, and healthcare professionals in the area. The flyers would provide information about both the inauguration and the services the MIC intends to offer.

MICs need to develop a set of minimum standards to ensure that performance of information services is continuously maintained at a high level. Quality assurance is valuable because it facilitates the identification and 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 (see Figure 11.2).

Financial support

Medicines information centers must have access to objective, independent, and self-sufficient resources. Financial support must be free of any bias.

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 medicine information services considered to be in the public domain, provided that the authorities respect the neutral, independent, and autonomous nature of 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 cover costs of utilities, such as electrical power and telephone services, regular 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, photocopier, fax machine, and telephone. Having a strategic plan and projected budgets in place provides evidence that the center will be sustainable and will be managed soundly. Budgets must contain both capital costs and operational costs (Figure 11.3).

Capital Costs

- Office space
- Furniture
- Equipment
- Initial investment in library resources

Operational Costs

- Salaries (staff and outside support)
- Staff training and education
- Maintenance of equipment
- Maintenance of office space
- Personnel resources—selection and training
- Telephone and postage
- Office supplies and photocopying costs
- Computer software upgrade
- Subscription costs for books, journals, compact discs, etc.

Figure 11.3
Capital and operational expenses for managing an MIC

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 come from several organizations; however, even 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 instructional materials.

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

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.

---

1. The terms MIC and DIC (drug information center) are used interchangeably in this document.

CHAPTER 12

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 national or, if applicable, local authorities. To authorize the marketing of a generic pharmaceutical product, MRAs are advised to require documentation indicating that the medicine was produced according to 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 products, 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, such as a biowaiver[1] based on the Biopharmaceutics Classification System (BCS) (United States Food and Drug Administration, 2003a). There are three types of bioequivalence studies: pharmacokinetic studies, the simplest and most often used in limited-resource countries; pharmacodynamic studies; and comparative clinical trials. In selected cases, an *in vitro* dissolution profile comparing the multisource (generic) product with the comparator product or dissolution studies may be sufficient to provide indication of equivalence.

Definitions

Throughout this chapter, discussions of bioavailability and bioequivalence will be based on the following definitions:

Bioavailability (BA). Bioavailability is the rate and extent of availability of an active pharmaceutical ingredient (API) 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 with the same active pharmaceutical ingredients(s) 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 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 medicine products (highly soluble, highly permeable), and for those that rapidly dissolve (85 percent or greater in 15 minutes or less in pH 1.2, 4.5, and 6.8) can assure equivalence between the multisource (generic) product and the comparator product (**United States Food and Drug Administration, 2001**; Lindenberg et al., 2004). When a medicine does not produce measurable concentrations in an accessible biological fluid, comparative pharmacodynamic studies are an alternative means 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 pharmaceutical dosage forms are considered to be equivalent without need for further documentation requirements or BE testing when the product in question contains the same API in the same molar concentration as the comparator product and essentially the same excipients in comparable concentrations (**Yu et al., 2002**):

- Aqueous solution for intravenous, intramuscular, or subcutaneous parenteral administration;
- Solutions for oral use, including syrups, elixirs, tinctures, or other soluble forms (but not suspensions), that contain only excipients known to have no effect on gastrointestinal (GI) transit or permeability, and hence, absorption or stability of the API in the GI tract;
- Powders for reconstitution as a solution and the solution meets either criterion above;

- Gases;
- Optical, ophthalmic, or topical products prepared as aqueous solutions;
- Solutions for aerosol or nebulizer inhalation products or nasal sprays prepared as aqueous solutions.

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 index (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, gels, and skin-inserted contraceptives).
- Modified-release pharmaceutical products designed to act by systemic absorption. In some instances, product marketing authorization may be based on *in vitro–in vivo* correlation information and *in vitro* data of modified-release medicine products provided it is not the first (original) approval of the modified-release dosage form.
- 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 medicines and dosage forms, documentation of equivalence may be assessed by the use of *in vitro* dissolution testing. Some examples follow:

- Medicine 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 medicine 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 medicine release mechanism.
- Biowaivers based on BCS.

Multisource (generic) products used in BE studies

Generic products used in BE studies for registration purposes should be identical to the pharmaceutical product intended for market or use. 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/BE studies should be taken from batches produced for sale.

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 match 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.

For many pharmaceutical products, however, 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 another national MRA with advanced regulatory control.

The U.S. Food and Drug Administration has created a list of approved medicine products with therapeutic equivalence that can be used for equivalence evaluations (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 (2002a). 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 aspects of 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 points: 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 one (1) predose sample, at least 1–2 points before Cmax, 2–3 points around Cmax, and 3–4 points during the elimination phase. In total, about 7–9 points should be taken for estimation of the required pharmacokinetic parameters. Some study protocols require that sampling points should include one (1) pre-dose sample, 3 points before Cmax, 3 points around Cmax, and 4–5 points during the elimination phase.

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 medicine (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: A 90% confidence interval (CI) 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 Harmonisation 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 products, 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.

To confirm that the 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).

---

1. Examples are acetylsalicylic acid, chloroquine (phosphate/sulfate), quinine, pyrazinamide, salbutamol (sulfate), stavudine (d4T), and zidovudine (ZDV or AZT).

CHAPTER 13

Rapid Assessment of Quality Assurance and Quality Control of Medicines

The quality and safety of medicines are becoming increasing concerns throughout the world, especially in developing countries. Adequate medicines legislation and regulation, a 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 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 in a gap in regulations and inconsistent enforcement of laws, which often lead to a lack of clarity and coherence in the medicines regulatory process.

All functions of a medicines regulatory authority must work jointly 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 postmarketing surveillance for quality, adverse drug reactions, and control of promotion and advertisement of pharmaceuticals.

Objectives of the Assessment

The purpose of assessing a country's medicines quality assurance (QA) and quality control (QC) systems for medicines is to:

- Determine whether or not an MRA has defined key functions and whether they are being implemented.
- Examine what approaches and mechanisms the country uses to ensure the quality of pharmaceuticals sold in the market and how the MRA carries out its responsibilities.
- Identify strengths and weaknesses of the country's medicines QA program and QC systems and the reasons they exist.
- Make 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 a QA assessment, as illustrated in Figure 13.1, is supported by four equally important components:

Premarketing quality assessment—assessment of medicine product quality, safety, and efficacy for registration or market authorization.

Regulatory functions—central administration (enabling the regulatory authority to function), government quality control or testing laboratory, inspection services, licensing of persons and pharmaceutical establishments, and product recall.

Technical elements—norms, standards, specifications and procedures, and good practices.

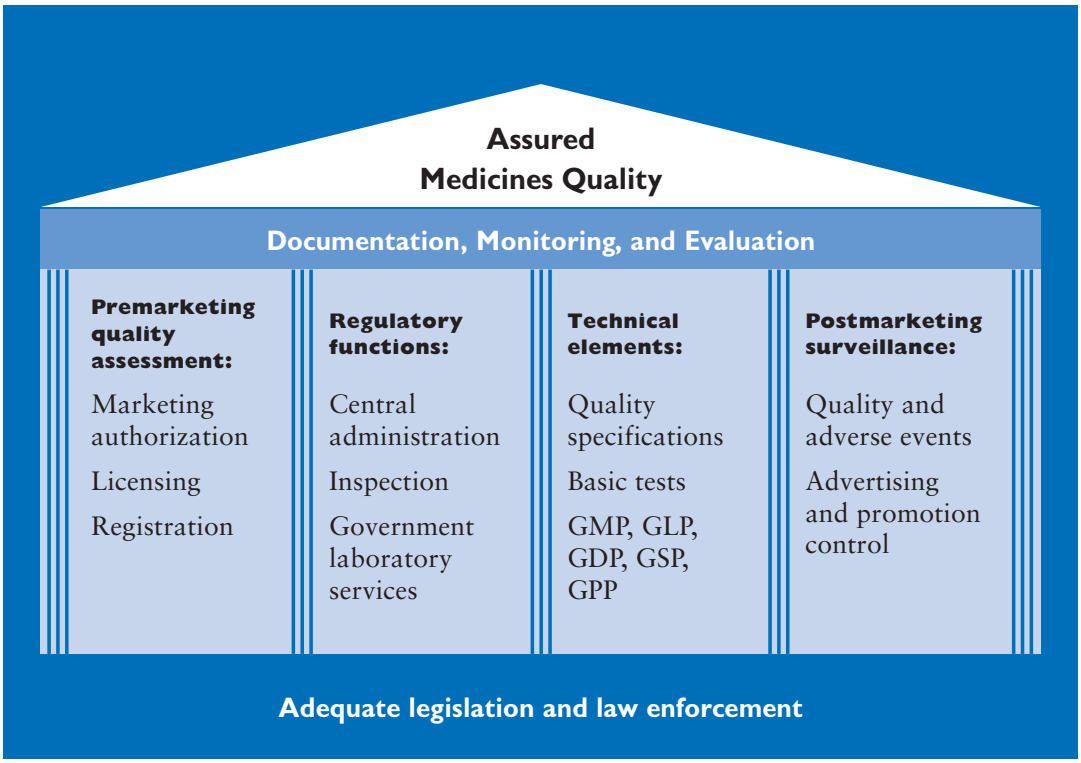


Figure 13.1
Structural components of a medicines quality assurance framework

GMP=good manufacturing practice; GLP=good laboratory practice; GPP=good pharmacy practice; GDP=good dispensing practice; GSP=good storage practice.

Postmarketing surveillance—monitoring for medicine quality and adverse events, and control of medicine promotion and advertising.

Figure 13.1 also illustrates the framework and the focus areas for data collection; the Rapid Assessment questionnaire parallels the structural components identified in Figure 13.1.

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 methods and techniques;
3. Data analysis methods; and,
4. Reporting and recommendations.

Planning for assessment

■ Establish an independent assessment team with a 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 medicines 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 nongovernmental or international organization.

The relevant authority must approve the assessment, including the appointment of the team, and its role and scope of work. In many instances, the Ministry of Health or MRA is responsible for approving the assessment; however, approval should be secured before any assessment activities begin.

■ Secure a financial budget based on the scope of work and timeframe described in the assessment.

■ Communicate information about the assessment to all agencies, responsible authorities, and interested persons to enlist support and cooperation. These usually include the different units of the MRA (e.g., medicines 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 structured questionnaire that assesses relevant factors may be used to guide reviewers through collection of the data and information required for the review and assessment (see Form G). Once analyzed, the data collected provides indicators of how well a system is working. Data collection may be carried out using a combination of techniques:

■ Consulting with key officials, which could include directors or deputies of primary divisions within the MRA, government, procurement agencies, selected nongovernmental organizations, medicines testing laboratories, and selected pharmaceutical establishments;

Methods for Data Analysis

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. These data can be tabulated and used in presentations to improve decision-making and outcomes.

Once collected and analyzed, the data may reveal relationships between certain data sets that help determine which aspects of a medicines regulatory system are working, and find a cause behind those that are not. Each aspect of the country's medicines quality assurance and control framework—premarketing quality assessment, regulatory functions, technical elements, and postmarketing surveillance—can be reviewed and changes suggested to improve efficiency.

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, medicines 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 medicines 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 malaria 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.

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.

- Reviewing both published and unpublished technical documents, as well as records from primary and secondary sources, which might include medicines laws, executive orders, inspection records, MRA and national laboratory annual or midterm reports, and economic, health, and medicine-related indicators; and,
- Using other convenient techniques, such as email, fax, and telephone.

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 process should be described.

ANNEX 6.1

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

General considerations

Immediately upon receiving the goods, whether in the central medical stores (CMS) or at the port of entry (sea, land, or air), sampling should be performed. The appropriate sampling method and procedure take into account the following parameters, which determine the number of samples to be taken for testing:

- Types of products;
- Size of consignment and the similarity and uniformity of contents; and,
- Product packaging.

The unit being sampled may be the transport container, for instance, 20 packs shrink-wrapped or boxed together, or an individual container. The required number of unit dosage forms is then withdrawn from any individual container in the selected transport container.

Generally, the number of units of individual samples is determined by the requirements of the analytical procedure used to test the product. Minimum key tests should include (a) appearance, (b) identity, (c) dissolution and, (d) assay for content of active pharmaceutical ingredients(s) (API). Ideally, each sample is examined to ensure that it is intact and the container checked for possible damage. The contents are inspected for uniformity and tested for identity. Usually, three independent samples (two for testing and one for retention) are taken from different, randomly selected 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, as long as previous experience with the product and the manufacturer has been favorable and there is evidence that the batches were produced at approximately the same time.

Sampling special precautions

A standard operating procedure should be in place that describes both the sampling process and the health and safety aspects of sampling.

The personnel carrying out the sampling should be trained in proper sampling techniques and procedures to minimize the introduction of bias. 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 an MRA official in the presence of an official from the central medical store, if applicable, and the consignee.

A "Note for the Record," including the information listed below, should be drawn up immediately and signed by the officials and representatives present during the collection of the samples:

- Date and time the samples were taken and the exact location;
- Product name and batch or lot, airway bill, and packing list numbers;
- Number of units (tablets, capsules, etc.) or blister packs taken; and,
- Observations (see first steps in three-level testing approach, Chapter 8).

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

Number of samples to be taken

From every batch or lot, three samples each should be taken, at a minimum, of 50 dosage units (tablets, capsules, or suppositories, etc.) for single API solid dosage forms, and 100 dosage units for fixed-dosed combinations (FDCs), that is, single preparations that contain more than one API. For products in vials, 10 vials per sample should be collected for single API injectables and 20 for FDCs.

Packaging and labeling of samples

The container used to store a sample neither should interact with the sampled material nor should it allow contamination. The samples should be in their original "unit" packaging and labeling, which should 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 blister-pack 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 measures must be taken to ensure that samples are properly packed and labeled so they can be transported to their testing location without any physical damage to the samples that could affect the physical/visual examinations and the integrity of the products.

- One sample goes with the necessary papers (e.g., sample collection form and testing request form) to the testing laboratory for analysis.
- Two samples are stored under controlled and prescribed conditions at the MRA or by the procurement agency for future analysis in case (a) laboratory analysis results in "Out of Specifications" (OoS) or (b) future problems occur with the products.
- The manufacturer or supplier should be notified immediately that samples have been taken, indicating which batch numbers were sent for laboratory analysis and copied on test results, regardless of the outcome.
- The purchase contract should included procedures on how to handle cases of OoS outcome, e.g., recall, replacement of defective goods, destruction of defective goods, financial indemnification, etc.

The same procedure should apply for transporting samples for confirmatory testing at a reference laboratory.

Storage of samples

Collected samples must be properly packed, transported, and stored in order to prevent any deterioration, contamination, or adulteration. Collected samples should be stored according to their specific storage instructions. Closures and labels should be tamper-evident, that is, of a type that reveals unauthorized opening. 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, product samples may arrive in pallets, cartons, or boxes. The inspector or sample collector should have all necessary papers in hand—packing list and airway bill—throughout the shipment inspection and sample collection.

1. **Step One:** Physical count and determination of items and batches
   - 1.1. Determine how many medicines (items) are in the cartons or boxes.
   - 1.2. Determine how many batches per medicine are in the consignment.
2. **Step Two:** Selection of cartons or boxes for physical examination
   - 2.1. Randomly select boxes for examination; if some boxes appear suspect, additional boxes should be examined.
   - 2.2. Examine damages to the outside of boxes or cartons.
     - Check physical conditions of cartons or boxes in each pallet.
     - Check packaging for damages.
     - Check that the overall labeling of cartons or boxes matches the packing list.
   - 2.3. Document the damages or defects.
3. **Step Three:** Visual inspection of inner boxes
   - 3.1. Open the boxes selected in Step Two, and perform the following tasks:
     - Check the condition of the unit packs for integrity of the packaging material.
     - Check the overall labelling of unit packs for the medicine name, strength, dosage form, manufacture date, expiry date, etc.
     - Check the labels for spelling mistakes, damage, or anything suspicious.
     - Check the contents (tablets, capsules, blisters) for consistency of shape and color.
     - Count, categorize, and record the number of defects.
4. **Step Four:** Taking samples—use the "n" value (the number of samples to be taken) in the table below for laboratory testing and retention.

How to determine the number of units to sample

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

* The number expressed is applied per type of medicine in the consignment.

For further information 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.

Report on Suspected Adverse Drug Reaction

NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING*

Please report ALL suspected adverse drug reactions including those for traditional medicines. Do not hesitate to report if some details are not known. Identities of Reporter, Patient, and Institution will remain confidential.

A. Patient Information

Initial or R/N only:

Age:

Sex: ☐ M ☐ F

Weight:

Ethnic Group ☐ Malay ☐ Chinese ☐ Indian
☐ Other, please specify:

Hospital/Clinic:

B. Adverse Reaction Description

Time to onset of reaction (hours/days):

Date of reaction:

Reaction subsided after stopping drug/reducing dose:
☐ Yes ☐ No ☐ Unknown

Reaction reappeared after reintroducing drug:
☐ Yes ☐ No ☐ Unknown

Extent of reaction:
☐ Mild ☐ Moderate ☐ Severe

Treatment of adverse reaction:

Outcome: ☐ Recovered ☐ Unknown ☐ Not yet recovered ☐ Fatal–date of death

Drug reaction:

Relationship: ☐ Certain ☐ Probable ☐ Possible ☐ Unlikely ☐ Unclassifiable

Form A
Sample Adverse Drug Reaction Reporting Form

*From Malaysian Adverse Drug Reactions Advisory Committee (MADRAC), National Pharmaceutical Control Board of Malaysia. The National Drug Safety Monitoring Centre, secretariat to MADRAC, is a member of the World Health Organization Programme for Drug Monitoring. Reporting form can be found online: www.bpfk.gov.my/madr.

C. Drug Details

Suspected drug, and all other drugs used:

Dosage Given:

Frequency:

Route:

Product Reg. No.:

Manufacturer:

Therapy Date Start:

Therapy Date Stop:

Indication:

Total drugs:

D. Relevant Investigations/Laboratory Data

E. Relevent History (e.g. hepatic/renal dysfunction, allergies, etc.)

F. Reporter

Name:

Date:

Designation:

E-mail:

Address:

Telephone:

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

Model Certificate of a Pharmaceutical Product

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes on page 135).[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 ☐ Unkown (key in as appropriate)

If the answer to 1.2 is Yes, continue with section 2A and omit section 2B.[6]

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

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: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/modelcertificate.

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

Model Statement of Licensing Status

This statement conforms to the format recommended by the World Health Organization (general instructions and explanatory notes on page 138).

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:

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.

This **model certificate** is available on the WHO/EDM website at: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/model_license.

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

Manufacturer's Official Batch Certificate of a Pharmaceutical Product

This certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes on page 141).

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/areas/quality_safety/regulation_legislation/certification/modelbatch.

Form E
Sample questionnaire for prequalification of suppliers for pharmaceutical procurement

Sample questionaire 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 serves 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
Part IV	Product 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: Email:

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 percentage 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 which 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 as to 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 the product(s) 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:

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)

III. 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 which quality tests you perform 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 No, explain your way of sampling:

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

☐ Yes ☐ No

If No, 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 recorded:

- ☐ 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 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:

IV. 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 (see Form B)

☐ 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 approved manufacturing formula(s) 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 percent for the assay in active ingredient(s):

☐ 95–105% ☐ 90–110% ☐ Other:

Additional specifications to those in the pharmacopeia:

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°C/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: _____

Form F
Drug Information Center Assessment Questionnaire

Drug Information Center Assessment Questionnaire

INTRODUCTION

The quality, safety, and informed use of medicines are very important for establishing a successful health care system; however, many health care facilities around the world—especially those in resource-limited countries—lack one or more elements. Drug information is an integral part of a health care system, and a drug information center (DIC) should be established to meet the drug information needs of health care professionals and patients within the scope of a health care facility.

A DIC should be able to provide drug information consults; support Pharmacy and Therapeutics (PNT) committees; manage formulary revisions; develop policy and procedures; generate drug therapy practice guidelines and drug formulary lists; sustain antibiotic management, Drug Usage Evaluation (DUE), and Adverse Drug Reaction (ADR) programs; and carry out other activities as needed.

Drug information consults are the primary objectives of a DIC; it should be able to:

- Provide comprehensive, objective, and unbiased information to health care professionals to aid decision-making and problem-solving.
- Provide drug information services to health care institutions for delivery of quality patient care.
- Teach pharmacy students, pharmacists, and other health care providers the skill of efficiently searching the literature, critically analyzing the information, and accurately communicating (both verbally and in writing) the results.
- Serve as an information resource center for faculty, students, and health care professionals.
- Conduct research for the advancement of drug information and pharmacy practice.

As part of a successful health care system, a DIC can assist prescribers in determining which medications should be recommended for formulary status by developing drug literature evaluations and/or formulary class reviews. This is especially important in referral and central hospitals. An individualized formulary can be developed from the DIC's database, which can be tailored to the subscriber's needs.

A DIC should be able to publish regular newsletters to notify pharmacists and other health care professionals of recently published pharmacy/biomedical literature. A DIC should also be able to publish additional newsletter editions to notify health care professionals of breaking news or other pertinent information, new drug reviews, drug class reviews, new breakthroughs in medicine or current topics of interest.

Also, a DIC has to provide committee support and participate in the development of standard treatment guidelines that incorporate current, relevant, and comprehensive information to provide appropriate drug therapy for patients.

Once a DIC is well established, it should be able to assist with the antibiotic management program that addresses the prevention of resistance and provides quality patient care. A DIC can also provide information to assist in the daily activities of pharmacy practice, including patient drug information and/or disease information sheets, and information for compliance with pharmacy laws and regulations.

A DIC should undertake a number of commitments and responsibilities; such accomplishments define the success or failure of a DIC in meeting its objectives. The following questions are designed specifically to assess the capacity of a DIC.

OBJECTIVES

1. Determine the existence of a functional or operational DIC in a given health care facility;
2. Examine what approaches and mechanisms the DIC uses to disseminate drug information to health care professionals, patients, and consumers;
3. Identify strengths and weaknesses of the DIC, if a DIC exists in a given health care facility;
4. Make suggestions and, where appropriate, recommendations to a health care facility's directors, administrators, and chief pharmacists responsible for a DIC within the health care facility; and,
5. Determine what kind of assistance the U.S. Pharmacopeia Drug Quality and Information Program can deliver to the DIC in the health care facility.

QUESTIONNAIRE

This questionnaire is designed to obtain general background data and specific information for the review and assessment of a DIC within the confinements of a health care facility.

Part I: Background Information

Type of health care facility:		
Central referral hospital:	☐ Yes	☐ No
Specialized care hospital:	☐ Yes	☐ No
District hospital:	☐ Yes	☐ No
Rural hospital:	☐ Yes	☐ No
Health center:	☐ Yes	☐ No
Other (specify):		
Total number of beds:		

Type and number of health care professionals

Type of health care professionals	Number
☐ Medical doctors	Number:
☐ Pharmacists	Number:
☐ Nurses	Number:
☐ Others (specify):	Number:
	Number:

Type and number of physicians with specialized training

Type of specialized training	Number
☐ Allergy and immunology	Number:
☐ Cardiovascular medicine	Number:
☐ Emergency medicine	Number:
☐ Endocrinology	Number:
☐ Gastroenterology	Number:
☐ Hematology	Number:
☐ Infectious diseases	Number:
☐ Nephrology	Number:
☐ Neurology	Number:
☐ Obstetrics, gynecology and women's health	Number:
☐ Oncology	Number:
☐ Pediatrics	Number:
☐ Pulmonary and critical care medicine	Number:
☐ Rheumatology	Number:
☐ Others (specify):	Number:
	Number:

Existence of a Drug Information Center (DIC)

Does the health care facility operate a functional DIC? ☐ Yes ☐ No

If Yes, please describe its main duties, responsibilities, and functions:

If No, provide reasons:

Year the DIC was established:

Health care facility budget allocations for the DIC

Has the health care facility allocated a budget to the DIC? ☐ Yes ☐ No

If Yes, provide figures; if No, provide reasons:

Number of pharmacists trained to manage a DIC:

Place and duration of training:

Has the DIC received any kind of support (e.g., financial, technical, etc.) from any other source? ☐ Yes ☐ No

If Yes, indicate the type and financial value of the support:

Please specify the main constraints facing the DIC in conducting day-to-day activities:

Does the DIC support other health care facilities? ☐ Yes ☐ No

If Yes, provide the information below:

Name of Health Care Facility	Domestic	International

Does the DIC have a working relationship with the Ministry of Health (MOH) and/or the MRA? ☐ Yes ☐ No

If Yes, please specify:

Does the DIC have a working relationship with schools of pharmacy or medical schools? ☐ Yes ☐ No

If Yes, please specify:

Part II: Equipment and Furniture

Does the DIC have adequate equipment and furniture to operate? ☐ Yes ☐ No

If Yes, provide the type of equipment/furniture in the table below.

Type and number of equipment and/or furniture	Yes/No	Number
☐ Computers	☐ Yes ☐ No	
☐ Printers	☐ Yes ☐ No	
☐ Scanners	☐ Yes ☐ No	
☐ Shelves	☐ Yes ☐ No	
☐ Filing cabinets	☐ Yes ☐ No	
☐ Chairs	☐ Yes ☐ No	
☐ Tables	☐ Yes ☐ No	
☐ Others (specify below)	☐ Yes ☐ No	

Does the DIC have access to the Internet? ☐ Yes ☐ No

If Yes, please specify which type: ☐ High-speed/broadband ☐ Dial-up

Part III: Drug Information Resources

Pharmacopeias are a major source of drug information. Check which of the following pharmacopeias are officially accepted for use:

☐ British Pharmacopoeia (BP)	☐ Yes	☐ No
☐ United States Pharmacopeia (USP)	☐ Yes	☐ No
☐ European Pharmacopoeia (EP)	☐ Yes	☐ No
☐ WHO International Pharmacopoeia (IP)	☐ Yes	☐ No
☐ Others (specify):	☐ Yes	☐ No

UpToDate is computer subscription service specifically designed to answer clinical questions. Content is reviewed on a continuous basis, making current information available at the point of care.

Does the DIC have access to the UpToDate Database? ☐ Yes ☐ No

The Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) publishes the Red Book, which provides information on more than 200 childhood infectious diseases.

Does the DIC have access to the print or online version of the Red Book?

☐ Yes ☐ No

The Royal Pharmaceutical Society of Great Britain and the British Medical Association publish the British National Formulary (BNF) in print and electronically (eBNF).

Does the DIC have access to the print or online version of the BNF?

☐ Yes ☐ No

A number of professional health-related organizations, health agencies, and others supply drug and/or medical information online.

Does the DIC have access to any of these online resources? ☐ Yes ☐ No

If Yes, please specify:

Micromedex is a comprehensive source of information for DICs. Does the DIC have access to the print and/or online versions of Micromedex? ☐ Yes ☐ No

If Yes, provide the type of information in the table below.

Type of information	Yes/No
☐ CareNotes	☐ Yes ☐ No
☐ DiseaseDex Emergency Medicine	☐ Yes ☐ No
☐ DiseaseDex General Medicine	☐ Yes ☐ No
☐ DrugDex	☐ Yes ☐ No
☐ Drug-Reax System	☐ Yes ☐ No
☐ IV Index System	☐ Yes ☐ No
☐ KinetiDex System	☐ Yes ☐ No
☐ Lab Advisor	☐ Yes ☐ No
☐ P&T QUIK Reports	☐ Yes ☐ No
☐ PoisonDex System	☐ Yes ☐ No
☐ ReproRisk System	☐ Yes ☐ No
☐ USP DI	☐ Yes ☐ No
☐ Others (specify):	☐ Yes ☐ No

Part IV: DIC Services

Which of the following drug information requests from health care professionals are covered by the DIC:

☐ Drug therapy/Pharmacotherapy	☐ Yes	☐ No
☐ Medication dosing	☐ Yes	☐ No
☐ Drug interactions	☐ Yes	☐ No
☐ Product availability	☐ Yes	☐ No
☐ Drug-induced adverse effects	☐ Yes	☐ No
☐ Product identification	☐ Yes	☐ No
☐ Generic drug bioequivalence	☐ Yes	☐ No
☐ Pharmacokinetics	☐ Yes	☐ No
☐ Pharmacodynamics	☐ Yes	☐ No
☐ Pregnancy/Lactation	☐ Yes	☐ No
☐ Compounding	☐ Yes	☐ No
☐ IV compatibility	☐ Yes	☐ No
☐ Regulatory affairs	☐ Yes	☐ No
☐ Others (specify):	☐ Yes	☐ No

Which of the following activities are performed by the DIC:

☐ Develop and print computerized formulary	☐ Yes	☐ No
☐ Publish weekly newsletters	☐ Yes	☐ No
☐ Publish quarterly newsletters	☐ Yes	☐ No
☐ Develop treatment recommendations	☐ Yes	☐ No
☐ Develop DUR criteria and analysis	☐ Yes	☐ No
☐ Provide committee support	☐ Yes	☐ No
☐ Assist the antibiotic management program	☐ Yes	☐ No
☐ Provide pharmacy practice materials	☐ Yes	☐ No
☐ Computer modeling for cost containment	☐ Yes	☐ No
☐ Others (specify):	☐ Yes	☐ No

Form G
Rapid Assessment of QA/QC—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 in Chapter 13 (pages 124–127).

Every effort has to be made to obtain the most up-to-date data and information. If multiyear 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; and,
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 1,000 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 for which the data apply.

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 active pharmaceuticcal ingredients (API)	
f. Total value of exports of finished pharmaceutical products	
g. Total value of exports of APIs	

5. Country health and pharmaceutical human resources

Type and number of health professional training schools	Year
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	Other	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, and 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 adverse drug reactions	☐ 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 past three years?

☐ Yes ☐ No

If yes, provide figures in the following table.

Year	Government budget (in US$)
Current year	
Last year	
The year before	

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:

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 past 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

a. Year (e.g., 2005)

b. Year (e.g., 2006)

c. Year (e.g., 2007)

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

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 postmarketing surveillance):

☐ Yes ☐ No

If Yes, provide name:

2. Professional qualification and the number of people working at central administration; provide year for which 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, provide 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 for which 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 tests 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 past 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 past 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 quantity of adequate lab equipment/instruments
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 workbook or worksheet
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 flammable 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 past 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 past three 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 approximate charge per inspection: US$

14. Existence of mechanism or system for monitoring 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 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 past three 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 the 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 provide name:

d. Was pre-shipment or post-shipment 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 the 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:

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 an 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 D) 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, 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, process-

ing, 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 (or strength). The content of the active ingredient per dosage unit is determined by the assay of the specific monograph and generally expressed in milligrams or units per dosage unit.

Dosage form. The form (tablet, capsule, injection) of a completed pharmaceutical preparation.

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 used especially 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 in 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. 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 distribution practices (GDP). The part of quality assurance that ensures that the quality of a pharmaceutical product is maintained through adequate control throughout the numerous activities that occur during the distribution process.

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.

The recognition of test data generated in accordance with the principles of GLP, and common acceptance of those principles by authorities in multiple countries, avoids duplication of testing, benefits animal welfare, reduces costs to industry and governments, facilitates information exchange, prevents barriers to trade, and contributes to the protection of human health and the environment.

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 for that 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; and,

(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, 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 from 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 regulatory activities associated with pharmaceuticals, including at least all of the following functions: mar-

keting 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, ensure 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.

Pharmacodynamics. 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 accepted 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 Pharmacopoeia,* 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 products 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 ensure 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 ensure 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 B. 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, 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 generally accepted 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 an analytical support of a specification proposed for a 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 B, C, and D)

BIBLIOGRAPHY AND REFERENCE LIST

Control Quest Inc. 2002. *Equipment Compliance Program Elements and Realization*. Available online: www.validationworld.com.

Ericson M., Webster C., and F., de Crémier. 2004. *Accelerated assessment and temporary marketing authorization in the European Union*. EU Legislation. Regul Aff J. September 2004.

Harris, Daniel C. 2003. *Quantitative Chemical Analysis*, 6th ed. New York: W.H. Freeman.

Huber, Ludwig. 1998. *Equipment Qualification in Practice*. LC/GC Magazine 1998:16;148–156. Available online: www.labcompliance.com.

Huber, Ludwig. 2001. *Qualification of Equipment and Computerized Systems*. Pharmaceutical Canada 2001:2 (3);17/20. Available online: www.labcompliance.com.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1995. *ICH Harmonised Tripartite Guideline. Structure and Content of Clinical Study Reports E3*. Geneva: ICH Secretariat.

International Organization for Standardization. 2000. ISO Standards Handbook: *Statistical methods in general; Terminology and symbols; Acceptance sampling*. Ed. 5. Geneva: International Organization for Standardization.

International Pharmaceutical Federation. 1997. *Standards for Quality of Pharmacy Services: Good Pharmacy Practice*. The Hague: International Pharmaceutical Federation.

International Pharmaceutical Federation. 1998. *Good Pharmacy Practice in Developing Countries*. The Hague: International Pharmaceutical Federation.

Jahnke, M. 2005. *Quality Assurance Workbook for Pharmaceutical Manufacturers,* River Grove, IL: Davis Healthcare International Publishing, LLC.

Jayasuriya, D.C. 1985. *Regulation of pharmaceuticals in developing countries*. Geneva: World Health Organization.

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

Johnson, K.W. 1999. *Providing unbiased drug and therapeutic information*. Proceedings: Modern Aspects of Professional Drug Information. Chisinau, Moldova, June 22–24.

Kasim, N.A., M. Whitehouse, C. Ramachandran, et al. 2004. *Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification*. Mol Pharm 2004;1:85–96.

Lindenberg, M.,S. Kopp, and J.B. Dressman. 2004. *Classification of orally administered drugs on the World Health Organization model list of essential*

All URL addresses use the hypertext transfer protocol (http) and are current as of October 2007. Some publication URLs have been truncated to the organization home site to minimize inactive links.

medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharm 2004; 58:265–278.

Malaysia National Pharmaceutical Control Bureau. 2003. *Report on Suspected Adverse Drug Reactions*. National Centre for Adverse Drug Reactions Monitoring. Interactive form available online: www.bpfk.gov.my/madrac%20-%20reporting%20online.htm.

Management Sciences for Health. 1997. Managing *Drug Supply: The Selection, Procurement, Distribution and Use of Pharmaceuticals,* 2nd ed. West Hartford, Conn.: Kumarian Press

Palylyk-Colwell, E., F. Jamali, W. Dryden, E. Friesen, et al. 1998. *Bioequivalence and Interchangeability of Narrow Therapeutic Range Drugs*. Canadian Society for Pharmaceutical Sciences Discussion. J Pharm Pharm Sci. 1998;1:2–7. Available online: www.ualberta.ca.

Phanouvong, S., H. Vrakking, L. Blanc, E. Wondemagegnehu, T. Moore, L. Rgo, et al. 2002. *Operational guide for national tuberculosis programmes on the introduction and use of fixed-dose combination drugs* (WHO/CDS/TB/2002. 308; WHO/EDM/PAR/2002.6). Geneva: World Health Organization.

Ratanawijitrasin, S., and E. Wondemagegnehu. 2002. *Effective Drug Regulation. A Multi-Country Study.* Geneva: World Health Organization.

Rational Pharmaceutical Management Project. 2000. *A Technical Review of Antimicrobial Drug Information in Selected Countries*. Rockville, Md.: U.S. Pharmacopeia.

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

Turner, L. 1999. *Drug Information Center Management Training Course: General Manual* (draft). Rockville, Md.: U.S. Pharmacopeia.

United Nations Development Programme. 2005. *General business guide for potential suppliers of goods and services*. Copenhagen: UNDP/ Inter-Agency Procurement Services Office. Available online: www.iapso.org/supplying/business.asp.

United States Food and Drug Administration. 1996. *Equipment & Calibration*. In Medical Device Quality Systems Manual: A small entity compliance guide, 1st ed. (HHS Publication FDA 97-4179). Rockville, Md: U.S. Food and Drug Administration, Center for Devices and Radiological Health, Office of Health and Industry Programs. Available online: www.fda.gov/cdrh/.

United States Food and Drug Administration. 2001. *Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system*. Available online: www.fda.gov/cder/guidance/.

United States Food and Drug Administration. 2003a. *The Biopharmaceutics Classification System (BCS) Guidance*. Rockville, Md: U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science. Available online: www.fda.gov/cder/OPS/BCS_guidance.htm.

United States Food and Drug Administration. 2003b. FDA *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products: General Considerations*. Available online: www.fda.gov/cder/guidance/.

United States Food and Drug Administration. 2004. *Approved Drug Products with Therapeutic Equivalence Evaluations,* 24th ed. Rockville, Md.: U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Available online: www.fda.gov/cder/ob/.

United States Pharmacopeia. 2007a. *Good Manufacturing Practices for Bulk Pharmaceutical Excipients, United States Pharmacopeia 27–The National Formulary 22 (USP–NF)*. Bethesda, Md.: Rockville, Md: The United States Pharmacopeial Convention.

United States Pharmacopeial. 2007b. *Good Packaging Practices, United States Pharmacopeia 30–The National Formulary 25 (USP–NF)*. Rockville, Md.: The United States Pharmacopeial Convention.

United States Pharmacopeia. 2007c. *United States Pharmacopeia 27–The National Formulary 22 (USP–NF)*. Bethesda, Md.: Rockville, Md: The United States Pharmacopeial Convention.

United States Pharmacopeia Drug Quality and Information Program. 2006. *Guidelines for Drug Sampling: USP DQI Drug Quality Monitoring Program/Use of Basic Tests at the Peripheral Level*. Rockville, Md.: The United States Pharmacopeial Convention. Available online: www.usp.org/worldwide/dqi/resources/assessmentMaterials.

United States Pharmacopeia Drug Quality and Information Program. 2007. *Rapid Assessment of Medicines Quality Assurance and Medicines Quality Control*. Rockville, Md.: The United States Pharmacopeial Convention. Available online: www.usp.org/worldwide/dqi/resources/assessmentMaterials.

Winfield, A.J., and R.M.E. Richards. 2003. Dispensing techniques (compounding and good practice), *Pharmaceutical Practice,* 3rd ed. Oxford, UK: Churchill Livingstone.

World Health Organization. 1988. *Ethical Criteria for Medicinal Drug Promotion*. Geneva: World Health Organization.

World Health Organization. 1990. *WHO Expert Committee on Specifications for Pharmaceutical Preparations* (31st report, WHO Technical Report Series No. 790). Geneva: World Health Organization.

World Health Organization. 1991. *Basic Tests for Pharmaceutical Dosage Forms*. Geneva: World Health Organization.

World Health Organization. 1992. *Good Manufacturing Practices for Pharmaceutical Products* (32nd report, Annex 1, WHO Technical Report Series No. 823). Geneva: World Health Organization.

World Health Organization. 1994. *Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* (WHO/DAP/94.21). Geneva: World Health Organization.

World Health Organization. 1996a. *Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms* (WHO Technical Report Series No. 863). Geneva: World Health Organization.

World Health Organization. 1996b. *Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. WHO Expert Committee on Specifications for Pharmaceutical Preparations* (34th report, WHO Technical Report Series No. 863; pp. 155–177). Geneva: World Health Organization.

World Health Organization. 1996c. *WHO Expert Committee on specifications for pharmaceutical preparations* (35th report, WHO Technical Report Series no. 885, Annex 7). Geneva: World Health Organization.

World Health Organization. 1997a. *Quality assurance of pharmaceuticals: A compendium of guidelines and related materials, Vol. 1*. Geneva: World Health Organization.

World Health Organization. 1997b. *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Proposed guidelines for the certification of active pharmaceutical ingredients (*document WHO/PHARM/586 Rev.1). Geneva: World Health Organization.

World Health Organization. 1997c. *A WHO guide to good manufacturing practice (GMP) requirements: Part 2 Validation*. Geneva: World Health Organization. Available online: www.who.int/vaccines.

World Health Organization. 1998a. *Good manufacturing practices: Authorized persons—the role, functions and training. WHO Expert Committee on Specifications for Pharmaceutical Preparations* (35th report, WHO Technical Report Series No. 885). Geneva: World Health Organization.

World Health Organization. 1999a. *Counterfeit drugs: Guidelines for the development of measures to combat counterfeit drugs* (Essential

Drugs and Medicines Policy. WHO/EDM/QSM/9.1.). Geneva: World Health Organization.

World Health Organization. 1999b. *Effective drug regulation: What can countries do?* (discussion paper). (Essential Drug and Medicines Policy WHO/HTP/EDM//MAC(11)99.6.) Geneva: World Health Organization.

World Health Organization. 1999c. ***Guidelines for Drug Donations*, 2nd ed.** (Supply and Marketing Interagency Guidelines; WHO/EDM/PAR 99.4). Geneva: World Health Organization. Available online: http://whqlibdoc.who.int/hq/1999/WHO_EDM_PAR_99.4.pdf

World Health Organization. 1999d. *Marketing authorization of pharmaceutical products with specific reference to multi-source (generic) products: A manual for a drug regulatory authority.* (Regulatory Support Series, No. 5. WHO/DMP/RGS/98.5.) Geneva: World Health Organization.

World Health Organization. 1999e. *Establishing the bioequivalence of rifampicin in fixed-dose formulations containing isoniazid with or without pyrazinamide and/or ethambutol compared to the single drug reference preparations administered in loose combination. Model Protocol* (WHO/CDS/TB/99.274; 1999). Geneva: World Health Organization, Communicable Diseases Cluster.

World Health Organization, United Nations Children's Fund, United Nations Population Fund, The World Bank. 1999. *Operational principles for good pharmaceutical procurement: Interagency guidelines* (WHO/EDM/PAR /99.5). Geneva: World Health Organization.

World Health Organization. 2000b. *Safety Monitoring of Medicinal Products. Guidelines for setting up and running a Pharmacovigilance Centre*. World Health Organization and the Uppsala Monitoring Centre, Available online: www.who-umc.org/graphics/4807.pdf.

World Health Organization. 2000c. *Quality assurance of pharmaceuticals: A compendium of guidelines and related materials — Good manufacturing practices and inspection, Vol. 2*. Geneva: World Health Organization. Available online: www.who.int/publications/.

World Health Organization. 2002a. *Expert Committee on Specifications for Pharmaceutical Preparations* (WHO Technical Report Series 902). Geneva: World Health Organization.

World Health Organization. 2002b. *Good Practices for National Pharmaceutical Control Laboratories* (WHO Technical Report Series 902). Geneva: World Health Organization.

World Health Organization. 2002c. *How to develop and implement a national drug policy*, 2nd ed. Geneva: World Health Organization.

World Health Organization. 2002d. *Practical Guidelines on Pharmaceutical Procurement for Countries with Small Procurement Agencies*. Manila: WHO Regional Office for the Western Pacific.

World Health Organization. 2003a. *Application of Hazard Analysis and Critical Control Point (HACCP) Methodology to Pharmaceuticals (Annex 7). WHO Expert Committee on Specifications for Pharmaceutical Preparations* (37th report, WHO Technical Report Series, No. 908.) Geneva: World Health Organization.

World Health Organization. 2003b. *Effective Medicines Regulation: Ensuring Safety, Efficacy and Quality, WHO Policy Perspective on Medicines* (WHO/EDM/2003.2). Geneva: World Health Organization.

World Health Organization. 2003d. *The International Pharmacopoeia*, 3rd ed. Geneva: World Health Organization.

World Health Organization. 2004a. *The World Medicines Situation*. Geneva: World Health Organization.

World Health Organization. 2004b. *WHO Expert Committee on Specifications for Pharmaceutical Preparations* (39th report, WHO Technical Report Series, No. 929). Geneva: World Health Organization.

World Health Organization. 2005. *Guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations* (39th report, WHO Technical Report Series, No. 929, Annex 4). Geneva: World Health Organization.

World Health Organization. 2006a. *The Safety of Medicines in Public Health Programmes: Pharmacovigilance, an Essential Tool.* World Health Organization and Uppsala Monitoring Centre. Available online: www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

Yu, L.X., G.L. Amidon, J.E. Polli, et al. 2002. *Biopharmaceutics Classification System: The scientific basis for biowaiver extensions.* Pharm Res 2002;19:921–925.

Zhen, L.H. 2003. *Drug registration application in China.* J. Pharm. Pharm. Sci. 6(2):211–214. Available online: www.cspscanada.org.

INDEX

Page numbers in *italics* refer to boxed information or figures.

D

E

F

G

H

I

J

K

L

M

N

Q

R

S

List of additional documents provided on the Operational Guide CD-ROM

1. ICH, 1995. ICH Harmonised Tripartite Guidelines. Structure and Content of Clinical Study Reports E3. Geneva: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Secretariat. Accessed on Jan 3, 2007. url: http://www.ich.org/LOB/media/MEDIA479.pdf
2. IPF, 1998. Good Pharmacy Practice in Developing Countries: Recommendations for step-wise implementation. The Hague, International Pharmaceutical Federation. Accessed on Jan 3, 2007. url: http://www.fip.org/files/fip/Statements/latest/Dossier%20003%20total.PDF
3. Ratanawijitrasin, S., and Wondemagegnehu E., 2002. Effective Drug Regulation—A multi-country study. Geneva: World Health Organization.
4. US FDA, 2004. Approved Drug Products with Therapeutic Equivalence Evaluations, 24th ed. Rockville, MD, United States Food and Drug Administration Center for Drug Evaluation and Research. Accessed Jan 3, 2007. url: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm
5. US FDA, 2001. Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-released solid oral dosage forms based on a biopharmaceutics Classification System. Accessed on Jan 3 2007. url: http://www.fda.gov/cder/guidance/3618fnl.pdf
6. USP DQI, 2006. Guidelines for Drug Sampling: USP DQI Drug Quality Monitoring Program Use of the Basic Tests at the Peripheral Level. Accessed on Dec 12, 2007. url: http://www.usp.org/worldwide/dqi/resources/assessment Materials.html
7. WHO, 2005. WHO Guidelines for sampling of pharmaceutical products and related materials. WHO Technical Report Series No. 929. Annex 4. World Health Organization. Geneva. Accessed on Jan 2, 2007. url: http://whqlibdoc.who.int/trs/WHO_TRS_929-eng.pdf
8. WHO, 2004. Quality assurance of pharmaceuticals: A compendium of guidelines and related material. Vol. 2, updated edition—Good manufacturing practices and inspection. World Health Organization. Geneva. Accessed on Jan 2, 2007. url: http://whqlibdoc.who.int/publications/2004/9241546190.pdf
9. WHO, 2002. How to develop and implement a national drug policy. WHO Policy Perspectives on Medicines. Jan 2003, WHO, Geneva. Accessed on Jan 2, 2007. url: http://whqlibdoc.who.int/publications/924154547X.pdf
10. WHO, 2003. Guide to Good Storage Practices for Pharmaceuticals. Annex 9, WHO Technical Report Series, No. 908. World Health Organization Geneva. Accessed on Jan 2, 2007. url: http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf
11. WHO, 2003. Effective Medicines Regulation: Ensuring Safety, Efficacy and Quality. WHO Policy Perspectives on Medicines. Nov 2003, Geneva. Accessed on Jan 2, 2007. url: http://whqlibdoc.who.int/hq/2003/WHO_EDM_ 2003.2.pdf
12. WHO, 2002. Practical guidelines on pharmaceutical procurement for countries with small procurement agencies. World Health Organization for the Western Pacific Region, Manila. Accessed on Jan 3, 2007. url: http://www.wpro.who.int/NR/rdonlyres/7D1B522D-DEB1-48CB-88A7-68DEB599CCE1/0/pharmaProcure mentGuide.pdf
13. WHO, 2002. Good practices for national pharmaceutical control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO Technical Report Series No. 902. Annex 3, Geneva. Accessed on Jan 3, 2007. url: http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf
14. WHO, 1999. Pour une réglementation efficace des médicaments : que peut faire un pays ? [Effective drug regulation—What Can Countries do? (Document de fond] discussion paper). Essential Drug and Medicines Policy [Médicaments Essentiels et Autres. WHO/HTP/EDM/MAC(11)99.6, Geneva. Accessed on Jan 3, 2007. url: http://whqlibdoc.who.int/hq/1999/WHO_HTP_EDM_MAC(11)_99.6_fre.pdf
15. WHO, 1999. Guidelines for drug donations, 2nd ed. (Supply and Marketing Interagency Guidelines; WHO/EDM/PAR99.4), Geneva. Accessed on Jan 3, 2007. url: http://www.euro.who.int/document/EHA/PAR_ Donate_Guidelines.pdf
16. WHO, 1998. Marketing authorization of pharmaceutical products with special reference to multi-source (generic) products. A manual for a drug regulatory authority (Regulatory Support Series No. 5; document WHO/DMP/RGS/98.5), Geneva. Accessed on Jan 3, 2007. url: http://mednet3.who.int/prequal/info_general/ documents/WHO_DMP_RGS_98_5_R.pdf
17. WHO, 1996. Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Geneva. Accessed on Jan 3, 2007. url: http://www.who. int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html
18. WHO, 1996. Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO Technical Report Series No. 863. Annex 5, Geneva. Accessed on Jan 3, 2007. url: http://whqlibdoc.who.int/trs/WHO_TRS_863_(p1-p98).pdf

19. WHO, 2003. Good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908). Accessed on Jan 3 2008. url http://whqlibdoc.who.int/publications/2004/9241546190_part1.pdf.

20. WHO, 2001. WHO Expert Committee on Specifications for Pharmaceutical Preparations WHO Technical Report Series No. 908. Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva. Accessed on Jan 3 2008 at url http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf.

21. IPF, 1997. Good Pharmacy Practice in Developing Countries. The Hague: International Pharmaceutical Federation. Accessed on Jan 3 2008 at url http://www.fip.org/files/fip/Statements/latest/Dossier%20003%20total.PDF.

22. WHO, 1996. Good Pharmacy Practices in Community and Hospital Settings. (WHO/PHARM/DAP 96.1).

23. WHO, 1998. Good manufacturing practices: Authorized persons°™the role, functions and training. In WHO Expert Committee on Specifications for Pharmaceutical Preparations WHO Technical Report Series No. 885. Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fifth report. Geneva. Accessed on Jan 3 2008. url: http://whqlibdoc.who.int/trs/WHO_TRS_885.pdf

U. S. Pharmacopeia Drug Quality and Information Program




UNITED STATES PHARMACOPEIA
International Technical Alliances Program
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA
www.uspdqi.org