CHAPTER 19

Quality assurance for pharmaceuticals

Summary 19.2

19.1 Pharmaceutical quality 19.2
Pharmaceutical quality assurance framework • Defining and assessing pharmaceutical quality • Consequences of poor pharmaceutical quality • Determinants of pharmaceutical quality • Prevalence of poor-quality pharmaceuticals • Global quality-monitoring options

19.2 Practical approaches to quality assurance 19.8

19.3 Obtaining good-quality pharmaceuticals 19.10
Careful product selection • Careful supplier selection • Product certification • Product pedigrees • Batch certificates • DRAs and the procurement market today • Contract specifications

19.4 Verifying the quality of shipped products 19.15
Product identification technology • Inspection of shipments • Tiered pharmaceutical quality assessments • Laboratory testing

19.5 Maintaining pharmaceutical quality 19.17
Appropriate storage and transport • Appropriate dispensing and use • Pharmaceutical product presentations: treatment kits, co-packaging, and fixed-dose combinations

19.6 Monitoring pharmaceutical quality 19.18
Product problem reporting system • Product recalls

19.7 Personnel and training in the supply system 19.20

Assessment guide 19.21

References and further readings 19.21

ILLUSTRATIONS

Figure 19-1 Quality assurance framework 19.3
Figure 19-2 Determinants of pharmaceutical quality 19.6
Figure 19-3 Critical elements in quality assurance for pharmaceutical procurement 19.10
Figure 19-4 Sample medicine and supplier evaluation form 19.19

Table 19-1 Medicines found to have stability problems under tropical or high-temperature conditions 19.5
Table 19-2 Percentage of tracer medicines that failed quality testing in the public, private, and NGO sectors 19.8
Table 19-3 Comparison of certificates used in pharmaceutical procurement 19.14

BOXES

Box 19-1 Some substances exhibiting potential bioavailability problems in conventional oral forms 19.5
Box 19-2 Counterfeits and diversion from legal channels 19.9
Box 19-3 WHO's prequalification of medicines program 19.12
Box 19-4 Therapeutic window 19.16

COUNTRY STUDY

CS 19-1 Building quality assessment infrastructure in Tanzania 19.11

ANNEX

Annex 19-1 Resource organizations 19.22

SUMMARY

The purpose of quality assurance in pharmaceutical supply systems is to help ensure that each medicine reaching a patient is safe, effective, and of acceptable quality. A comprehensive quality assurance program includes both technical and managerial activities, spanning the entire supply process from pharmaceutical selection to patient use.

Established quality standards are published periodically in pharmacopoeias and in some government publications. For the purposes of primary health care, the most important characteristics of a pharmaceutical product are identity, purity, strength, potency, uniformity of dosage form, bioavailability, and stability.

Pharmaceutical quality is affected by starting materials, manufacturing process, packaging, transportation and storage conditions, and other factors; these influences may be cumulative.

If a pharmaceutical does not meet established quality standards, passes its expiration date, or has been degraded by storage conditions, the possible consequences are—

- Lack of therapeutic effect, leading to prolonged illness or death
- Toxic and adverse reactions
- Waste of limited financial resources
- Loss of credibility of the health care delivery system

A comprehensive quality assurance program must ensure the following—

- Pharmaceuticals selected have been shown to be safe and efficacious for their intended use, are presented in an appropriate dosage form, and have the longest possible shelf life.
- Suppliers with acceptable quality standards are selected.
- Pharmaceuticals received from commercial suppliers and donors meet specified quality standards at the time of delivery.
- Packaging meets contract and usage requirements.
- Repackaging activities and dispensing practices maintain quality.
- Storage and transportation conditions do not compromise product quality.
- Product quality concerns reported by prescribers, dispensers, and consumers are properly cataloged and addressed.
- Product recall procedures are implemented to remove defective products.

A quality assurance program should include training and supervision of staff members at all levels of the supply process and a suitable information system. Often, public officials must balance the costs of establishing and maintaining quality assurance systems against the benefits of having safe and effective medicines.

19.1 Pharmaceutical quality

As in most manufacturing processes, the quality of a final pharmaceutical product is determined by the starting materials, equipment, and technical know-how that go into producing and packaging it. Unlike a steel bolt or a tailored suit, however, a medicine is a dynamic product whose color, consistency, weight, and even chemical identity can change between manufacture and ultimate consumption. A medicine that passes all laboratory tests upon receipt may be useless within a few months if the packaging, storage, and transportation conditions are not maintained properly.

The purpose of quality assurance in pharmaceutical supply systems is to help ensure that each medicine reaching a patient is safe, effective, and of appropriate quality. The quality of pharmaceutical products is ensured by the technical and managerial activities of the quality system, which includes evaluating pharmaceutical product documentation, performing or reviewing quality-control laboratory tests, and monitoring product performance. Managerial activities include selecting reliable suppliers, preparing contract terms, monitoring supplier performance, and performing inspection procedures throughout the distribution network (Figure 19-1).

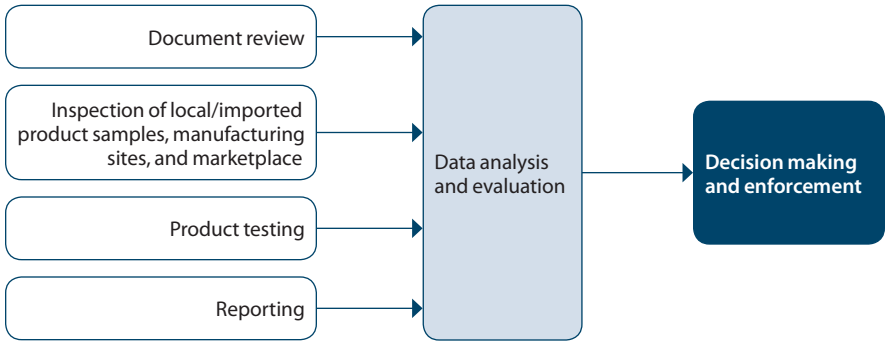
Note that quality assurance in pharmaceutical supply is not the same as quality control in manufacturing.

Pharmaceutical quality assurance framework

The following five elements are critical to achieving the expected treatment outcome. Using a pharmaceutical product to treat a patient presumes that the—

1. Active pharmaceutical ingredient (API) has been shown to be safe and effective for this treatment
2. Product is of suitable quality to provide an effective outcome
3. Prescriber has accurately identified the need for the treatment

Figure 19-1 Quality assurance framework



Source: CPM/MSH 2011.

4. Prescriber or dispenser has properly instructed the patient on how to use the product
5. Patient complies with the prescribed regimen correctly

The first two items are product-specific issues, which are the most easily addressed technically, whereas items three and four are practitioner-specific and depend on the practitioners' education, knowledge, and skill as well as the rigorous enforcement of performance standards. Item five is a patient-specific issue that depends on the patient's knowledge and commitment and the patient's access to services.

The safety and effectiveness of an API may be established either through a review of historical usage, such as in the case of digoxin's evolution from the foxglove plant (*digitalis purpurea*), or through complex procedures established for new chemical entities, such as those described by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

After the safety and effectiveness of an API has been approved for marketing in an ICH market region, other regions of the world follow with little or no additional assessment. The ICH economic zones (European Union, Japan, United States) perform almost 100 percent of the pharmaceutical research and consume over 85 percent (by value) of the pharmaceutical products in the world. These regions allocate large amounts of resources to ensure the safety and effectiveness of APIs granted market authorization in their zones. Once the safety and efficacy have been established through these procedures, other regions do not have to expend the same level of resources to establish these attributes. However, other product-quality issues, including bioavailability and bioequivalence, content uniformity, impurities and degradation, and medicine safety (pharmacovigilance), should be monitored on an ongoing basis in all market zones.

The complexity of globalized pharmaceutical markets and the difficulty in ensuring quality of imported products, including API, have been illustrated in headlines about deaths caused by adulterated products such as cough syrup in Peru and heparin in the United States—both tied to ingredients from China. As a result, the U.S. Food and Drug Administration (FDA) seeks to increase its global presence to make monitoring foreign manufacturers easier and to strengthen its involvement with harmonization of pharmaceutical standards (FDA 2010). In addition, the FDA wants to help build regulatory capacity in foreign counterparts. As part of that international effort, the agency has opened permanent offices in a number of cities around the world and has entered into dozens of agreements with other drug regulatory authorities (DRAs) to share inspection reports and other private information that can help improve the quality of pharmaceutical products worldwide.

The pharmaceutical regulatory and quality assurance processes that should be addressed by a country's DRA include (WHO 2004b)—

- Product registration: assessing and authorizing products for market entry and monitoring their safety and effectiveness after entry
- Regulation of manufacturing, importation, and distribution
  - Quality of manufacturing (good manufacturing practices)
  - Procurement integrity (assuring the qualifications of suppliers)
  - Quality of medicines in the distribution system (including product and premises inspection and product screening and testing)
- Regulation of medicine promotion and information: including postmarketing pharmacovigilance and consumer education

Of course, a country's quality assurance system is only as effective as its ability to monitor and enforce regulations. A country should address all issues at some level as part of a basic pharmaceutical quality assurance infrastructure;

however, in a resource-constrained setting, the risks to patients for each process must be assessed so resources can be allocated to focus on the most significant health threats.

Defining and assessing pharmaceutical quality

Pharmaceutical quality can be defined and tested in many ways. Quality standards are published periodically in pharmacopoeias and in some government publications, which provide detailed descriptions of pharmaceutical characteristics and analytical techniques. Standards may vary slightly from one pharmacopoeia to another, so a particular pharmaceutical may meet the standards of one pharmacopoeia and not those of another. When public standards have not been established, as is generally the case for newly marketed pharmaceuticals, analytical methods developed by the manufacturer and submitted as a part of the tender or marketing authorization requirements are usually applied.

The major pharmaceutical manufacturing and exporting countries publish their own pharmacopoeias, and on a regional basis, the *European Pharmacopoeia* establishes standards that are enforced by the governments of the European Union and others that adopt them. The *International Pharmacopoeia*, published by the World Health Organization (WHO), the *U.S. Pharmacopeia,* and the *British Pharmacopoeia* are used frequently by public-sector pharmaceutical supply programs in developing countries.

One important limitation of the *European Pharmacopoeia* is that it provides few specifications for individual dosage forms. The WHO *International Pharmacopoeia* (WHO 2008a) includes monographs on finished dosage forms, including antiretrovirals and newly developed antimalarial medicines. Analytical procedures in the *U.S. Pharmacopeia* tend to use complex and expensive technology, which may be beyond the reach of many developing countries. The European, Japanese, and U.S. pharmacopoeias are engaged in ongoing efforts to harmonize some of their standards, but progress is slow. Until common standards are finally achieved, purchasers must specify which dosage form standards are acceptable.

For pharmaceutical procurement organizations, pharmaceutical quality is assessed as the product's compliance with specifications concerning identity, purity, strength, potency, and other characteristics. Uniformity of the dosage form, bioavailability, and stability are important characteristics that are also considered in the specifications.

Identity. The identity test should confirm the existence of the active ingredient(s) indicated on the label. This characteristic is generally the easiest to check.

Purity. In addition to the API, most pharmaceuticals are made with ingredients added for bulk, consistency, or color that should not contain potentially harmful contaminants or microorganisms. The product should not have significant quantities of other products from cross-contamination.

Strength or potency. The medicine should contain the declared amount of API. Harmful by-products of degradation must be absent or should be below defined limits. Most pharmacopoeias specify an average content range, such as 90 to 110 percent of the amount written on the label, rather than an exact amount. To ensure a long shelf life, manufacturers often produce pharmaceuticals with the maximum allowable amount (for example, 110 mg rather than 95 mg), which provides a margin of safety for slight losses in strength or potency over time.

Uniformity of dosage form. The consistency, color, shape, and size of tablets, capsules, creams, and liquids should not vary from one dose to the next. Any lack of uniformity may suggest problems with other quality parameters such as identity, purity, or strength or potency. Lack of dosage uniformity may not influence the safety or effectiveness of a medicine, but it does reflect a lack of good manufacturing practices, which could influence the acceptability of a product to pharmacists, medical practitioners, and patients.

Bioavailability. *Bioavailability* refers to the speed and completeness with which a pharmaceutical administered in a specific form (tablet, capsule, intramuscular injection, subcutaneous injection) enters the bloodstream. The bioavailability of a product may depend on the other ingredients used in the formulation, such as solvents, binders, coloring agents, and coatings, or how ingredients are combined.

The comparative bioavailability of two pharmaceuticals is particularly important when a product that is usually purchased from one manufacturer is replaced with a product containing the same drug substance in the same dosage form, and in the same amount, but manufactured by a different firm. Even though the products both contain the correct amount of the API, the preparations may not give the expected therapeutic result if the API is released too quickly, too slowly, or incompletely when they are compared. Two pharmaceuticals are said to be *bioequivalent* and may be used interchangeably if both are absorbed into the bloodstream at the same rate and to the same extent.

Human bioequivalence studies are required for a number of medicines. Box 19-1 lists some medicines documented to have problems in bioavailability that require studies to determine the bioequivalence of products. Guidelines are available for the study of bioavailability, as well as specific bioavailability protocols for a small number of medicines (WHO/EURO 1988; USP 2007).

If purchasing is done through established and reliable suppliers, the bioavailability of most brand-name and generic medicines used in primary health care is sufficient to ensure that the patient receives the intended effect. Deciding which pharmaceuticals have a potential bioavailability problem is important, because manufacturers cannot supply clinical studies for all products, and government procurement programs generally cannot perform bioequivalence test-

Box 19-1
Some substances exhibiting potential bioavailability problems in conventional oral forms

API

- Aminophylline
- Ampicillin
- Carbamazepine
- Chloramphenicol
- Chloroquine
- Chlorpromazine
- Digitoxin
- Digoxin
- Dihydroergotamine
- Ergotamine
- Erythromycin
- Estrogens, conjugated or esterified
- Furosemide
- Glibenclamide
- Glyceryl trinitrate
- Griseofulvin
- Hydrochlorothiazide
- Iron sulfate
- Isosorbide dinitrate
- Levodopa
- L-thyroxine
- Methotrexate
- Methyldopa
- Nitrofurantoin
- Phenytoin
- Prednisolone
- Prednisone
- Quinidine
- Rifampicin
- Spironolactone
- Theophylline
- Warfarin

Source: WHO/EURO 1988.

ing. The Biopharmaceutical Classification System can help identify potential bioavailability problem products (Kasim et al. 2004). Where pharmaceutical registration systems exist, manufacturers or suppliers should be required to supply data on clinical studies whenever needed. Procurement agencies should also work with country DRAs and use their information in making decisions.

Stability. To be useful, a pharmaceutical must retain its properties within specified limits, such as particular storage conditions. The manufacturer and, in some cases, a country's DRA establish the time that a pharmaceutical's stability is under warranty, which ends with the expiration date. A product's stability depends on the active ingredient, which can be affected by its formulation and packaging. Improper storage and distribution can lead to physical deterioration and chemical decomposition, reduced potency, and occasionally, formation of toxic by-products of degradation. These effects are more likely to occur under tropical conditions of high temperature and humidity.

WHO has published a list of pharmaceutical substances that are less stable and therefore require particular attention (WHO 1990). However, few data are available on the stability of medicines under true field conditions. The ICH, whose members comprise experts from the major pharmaceutical manufacturing countries, has established guidelines on quality testing and storage in tropical regions (ICH 2003). WHO has been updating its stability guidelines with input from member country DRAs and in cooperation with ICH (WHO 2010d, 2009b). Several studies have examined the stability of a small number of essential medicines under tropical conditions of excessive temperature (over 40°C), high humidity, and inappropriate storage conditions (Gammon et al. 2008; Hogerzeil et al. 1991; Hogerzeil, Walker, and de Goeje 1993). Table 19-1 lists the medicines that have been found to have problems under tropical and high-temperature conditions.

Consequences of poor pharmaceutical quality

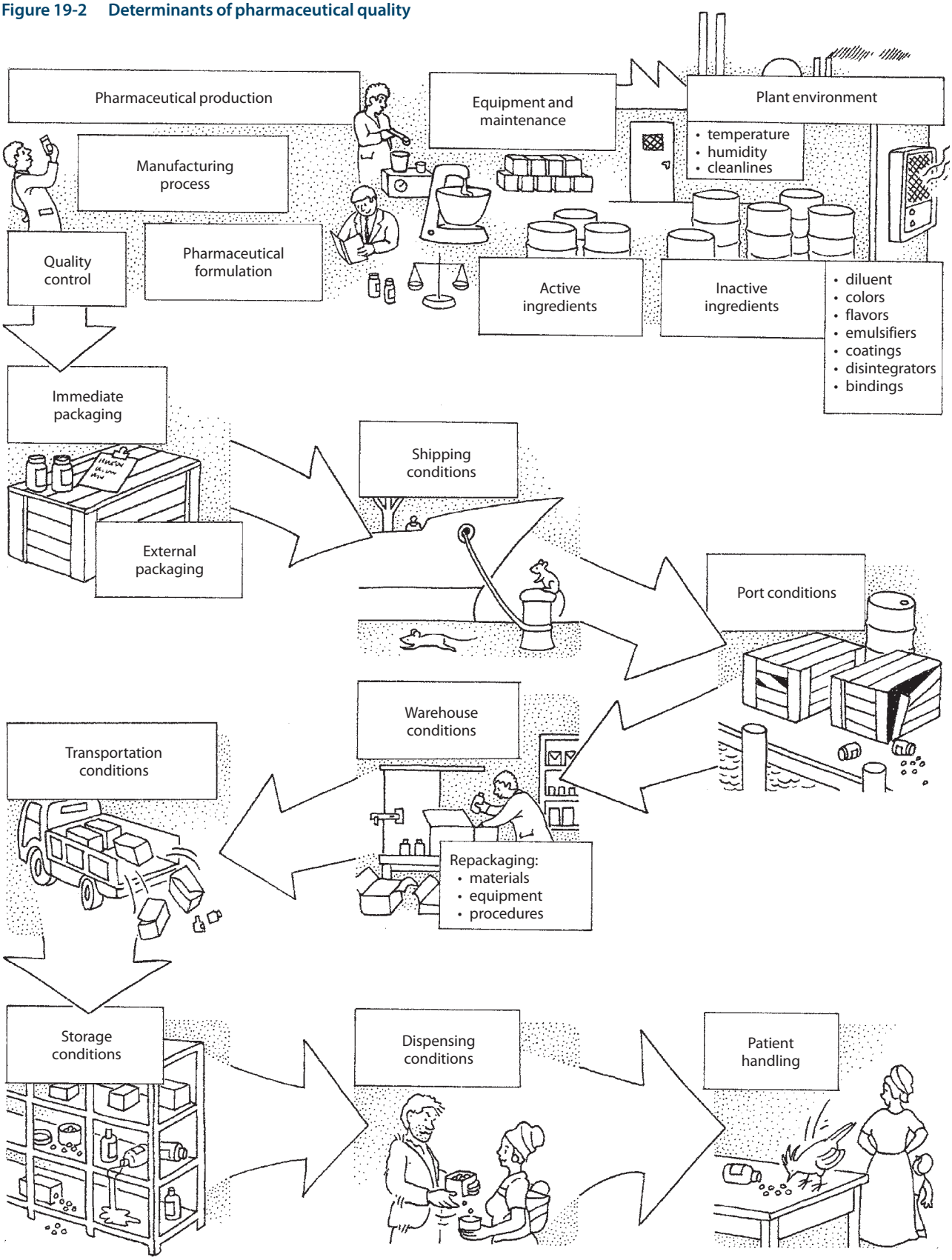
A poor-quality medicine is one that does not meet specifications. The use of poor-quality products may have undesirable clinical and economic effects, as well as affect the credibility of the health delivery system. Clinical effects can include prolonged illness or death or adverse reactions. On the economic side, limited financial resources may be wasted on poor-quality medicines.

Table 19-1 Medicines found to have stability problems under tropical or high-temperature conditions

Oral solids (tablets)	Oral liquids (syrups)	Inhalation	Injections/injectables
Acetylsalicylic acid	Paracetamol	Ipratropium	Ergometrine
Amoxicilline			Lidocaine
Ampicillin			Methylergometrine
Diltiazem			Succinylcholine
Lopinavir/ritonavir			Naloxone
Penicillin V			
Retinol			

Sources: Gammon et al. 2008; Hogerzeil et al. 1991; Hogerzeil et al. 1992; Hogerzeil, Walker, and de Goeje 1993; Pau et al. 2005.

Figure 19-2 Determinants of pharmaceutical quality



Lack of therapeutic effect may lead to prolonged illness or death. Poor pharmaceutical quality can sometimes lead to serious health consequences and death—for example, the use of poor-quality cardiac medicines and medicines for seizures and asthma. With others, such as cold remedies and minor painkillers, a reduction of up to 50 percent in the content of the active ingredient may not have serious consequences apart from ineffectiveness, although the best procurement policy requires all products to meet specifications.

Poor-quality pharmaceuticals may induce toxic or adverse reactions. When some products expire or are exposed to adverse climatic conditions (for example, excessive heat and humidity), they may undergo physical or chemical changes that can result in the formation of possibly toxic degradation products. Although fear of toxic pharmaceutical degradation in tropical climates is prevalent, tetracycline is the only common medicine in which it is known to occur. Excessive active ingredients may also lead to toxic or adverse reactions.

A much more frequent problem is contamination with microorganisms, usually bacteria or fungi. The consequences of this lack of sterility can be quite severe, particularly in the case of injectable medicines or in patients who are immunocompromised. Contamination of creams, syrups, and other medicines in jars and tubes is especially common in tropical environments, but the consequences vary, depending on the type of organism and the pharmaceutical involved. Errors in formulation and product contamination are uncommon with manufacturers who strictly comply with internationally accepted procedures and good manufacturing practices (GMPs). In practice, however, adherence to GMPs may vary from country to country, from manufacturer to manufacturer, or even between production runs at the same manufacturer. When contaminants are highly toxic or when toxic substances are inadvertently included in the product, the result can be catastrophic.

Poor pharmaceutical quality wastes money. Ineffective care or the need to treat adverse drug reactions resulting from poor product quality leads to more costly treatments. Poor pharmaceutical packaging casts doubts on product quality, leading to rejection by health personnel and patients. These products will then expire on the medical stores' shelves, wasting limited financial resources.

Poor pharmaceutical quality may seriously affect health system credibility. Patients and providers may suspect the quality of medicines when therapeutic failure or adverse drug reactions occur. Changes in product appearance, such as discoloration, crumbling of tablets, and hardening of oral suspensions, or changes in taste and smell rightly influence patients' perceptions of product quality. Patients may be discouraged from using health facilities, and worker morale may be affected, particularly if medicine shortages are also common.

Determinants of pharmaceutical quality

The quality of a medicine product coming off the production line is determined by the start-up materials, plant environment, manufacturing equipment, and technical know-how invested in developing and manufacturing the pharmaceutical. The medicine that ultimately reaches the patient, however, is further affected by packaging and by transportation and storage conditions.

These influences, especially factors in the manufacturing process, can be cumulative. For example, the excipient substances used to give tablets bulk and consistency may not affect the color, texture, or chemical quality of a pharmaceutical until the immediate container is opened in a hot, humid environment. Then, depending on the ingredients, the tablet may remain firm and dry or become moist and crumble within a matter of days. Factory humidity during packaging may also affect quality. If oral rehydration sachets are not packaged in a very low-humidity environment, moisture enters the sachet and may result in chemical or physical changes in the mixture that make it difficult to use. Similarly, the amount of grinding, thoroughness of mixing, choice of packaging, maintenance of packaging equipment, and other factors can have an effect that may not appear until the medicine reaches the point of consumption. Figure 19-2 summarizes these influences.

The dynamic nature of pharmaceuticals and the cumulative effects of the production process, right through to packaging, handling, transport, and storage conditions, require quality assurance at all levels in the pharmaceutical supply system (see *A Model Quality Assurance System for Procurement Agencies* [WHO/UNICEF/UNDP/UNFP/World Bank 2007]).

Prevalence of poor-quality pharmaceuticals

Data summarized in Table 19-2 indicate the extent of the pharmaceutical quality problem, as detected by pharmaceutical quality testing in the public, private, and nongovernmental organization (NGO) sectors of six countries.

In recent years, national and international authorities have recognized the emergence of counterfeit medicines as a serious problem. In most industrialized countries with effective regulatory systems and market control, the incidence of counterfeit medicines is an estimated 1 percent of market value (WHO 2010b). Therefore, most counterfeiting cases occur in developing countries—especially in Asia, where many of the counterfeit medicines are produced, and in Africa, where poverty and loose regulatory oversight make marketing of counterfeit products easier (see Box 19-2). However, counterfeiting is an increasing problem in all countries, including developed countries, where Internet purchases are popular. Over half of Internet medicine purchases from illegal websites are counterfeit (WHO 2010b).

Table 19-2 Percentage of tracer medicines that failed quality testing in the public, private, and NGO sectors

Country	Number of medicines	Number of samples	Public facilities	Private facilities	NGO facilities
Brazil (Minas Gerais)	8	64	13.6	9.1	10.0
Cambodia	14	132	13.0	9.6	7.7
El Salvador	10	87	50.0	28.6	27.3
Tanzania	10	110	12.9	13.0	0
Ghana	7	103	6.3	2.9	0
India (Rajasthan)	9	125	6.0	12.7	0

Source: CPM 2003a, 2003b, 2003c, 2003d, 2003e, 2003f.

Global quality-monitoring options

Currently, no global pharmaceutical quality standards exist, even for the APIs used in worldwide pharmaceutical product formulation, which are produced by only a few countries. However, the ICH processes to establish GMPs for APIs were more inclusive than any of the previous processes; for example, besides the usual ICH parties, representatives from the generics industry, the self-medication industry, and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme were included in the deliberations (ICH 2000).

These GMP standards are the world's first harmonized standards and have been adopted by the ICH regions and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme, in addition to WHO and many other countries. This harmonization implies that any DRA could perform an inspection of an API manufacturer and expect it to conform to these consensus GMPs. However, because almost all sovereign nations or market zones protect their local production of pharmaceutical products through selective tariffs and other mechanisms, no incentive exists for the development of a worldwide quality standard for APIs (Chapter 7). Some pharmacopoeias, including the *European Pharmacopoeia* and WHO's *International Pharmacopoeia,* have regional quality standards for many APIs; however, these pharmacopoeial standards have not been harmonized, resulting in varying specifications for APIs among regions (see Chapter 6 for more information on pharmacopoeias).

Because of the lack of harmonized standards, no basis exists for a pharmaceutical product common market with universal recognition of quality standards. The dearth of internationally recognized specifications leaves each market zone to establish its own specifications. Among the major pharmacopoeias, only the *British Pharmacopoeia* and the *U.S. Pharmacopeia* have standards for a significant number of products, and even they have essentially no specifications for products under patent protection in their markets.

19.2 Practical approaches to quality assurance

The procedures to establish a comprehensive quality assurance program can be divided into three categories—

1. Procedures to ensure that only medicine products that meet current standards for quality are bought. These include—
   - Careful product selection
   - Careful supplier selection
   - Certificate of analysis for each batch of product
   - Certification of good manufacturing practices
   - Batch certification (WHO-type certificate of a pharmaceutical product)
   - Inclusion of detailed product-quality specifications in the contract
2. Procedures to verify that shipped goods meet the specifications. These include—
   - Pre- and postshipment inspection
   - Analytical pharmaceutical testing
3. Procedures to monitor and maintain the quality of pharmaceuticals from the moment they are received until the medicine is finally consumed by the patient. These involve—
   - Proper storage and distribution procedures
   - Appropriate dispensing
   - Instructions to the patient on proper use of medications
   - Product defect and pharmacovigilance reporting programs

Few pharmaceutical management programs can effectively manage all the possible quality assurance activities for all the medicines that are procured. Consequently, realistic goals must be set to identify the combination of managerial and technical quality assurance activities that will be most effective under existing conditions. The critical elements in quality assurance for pharmaceutical procurement are listed in Figure 19-3, and Country Study 19-1 discusses how the Tanzania Food and Drugs Authority

Box 19-2
Counterfeits and diversion from legal channels

Recent examples of dangerous counterfeit medicines in the marketplace in countries worldwide include—

Southeast Asia: Of 391 samples of artesunate, 50 percent had little or no active ingredient and a wide range of wrong ingredients, including banned pharmaceuticals (Newton et al. 2008).
Madagascar, Senegal, and Uganda: Of 197 antimalarial samples from the public and private sectors that underwent full laboratory quality-control testing, the failure rates from Senegal, Madagascar, and Uganda were 44 percent, 30 percent, and 26 percent, respectively (USP and USAID 2009).
United States: The FDA warned consumers about 24 websites selling counterfeit medicines (FDA 2007).
Democratic Republic of Congo: The antidepressant fluvoxamine and the muscle relaxant cyclobenzaprine HCl had been labeled and sold as commonly prescribed antiretrovirals for HIV/AIDS treatment (Ahmad 2004).
Niger: Up to 2,500 people reportedly died after being given a fake meningitis vaccine (WHO 2003).

WHO defines counterfeit medicines as those that are "deliberately and fraudulently mislabeled with respect to identity and/or source" (WHO 2010c). Within this broad definition, it is useful to consider different categories of counterfeiting activities—

- Professional counterfeit organizations have modern production facilities capable of manufacturing products and labeling strikingly similar to the authentic products. They operate in the most lucrative markets—mostly developed countries.
- Mediocre counterfeit organizations produce poorly made look-alike products that in a side-by-side comparison can be discerned from legitimate products.
- Minor relabelers distribute to only a few outlets in an attempt to preserve the value of their outdated inventory by relabeling expired products with valid expiration dates and the same product name.
- More advanced or major petty relabelers deal in a secondary pharmaceutical market for outdated products primarily obtained from legitimate sources in developing and developed countries but distributed mostly in developing countries.
- Substitution counterfeiters place lower-priced finished dosage forms into more expensive packaging for marketing at higher prices. These relabeled outdated products may be distributed in developing or developed countries.

Formulating counterfeiters generally do not include the active pharmaceutical ingredient in the formulation. Substitution counterfeiters generally use the wrong medicine, whereas the relabelers generally have the right API present in about the right amount. Therefore, relabelers are the most difficult to detect, if their labeling is well done. Generally, most counterfeits have flawed labels that can help identify them as substandard. If the pharmaceutical product is provided without its original label, however, this feature may not always be helpful in identifying counterfeit products. Local or within-country counterfeit marketing depends on astute practitioners and consumers for detection and a good internal communication system to support prompt legal action.

The different characteristics of counterfeiters can be roughly summarized as follows in the table below.

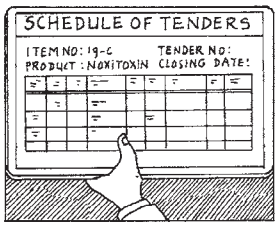
In 2006, WHO launched the International Medical Products Anti-Counterfeiting Taskforce, which is WHO's primary channel for anti-counterfeit activities.

Category	API[a]	Distribution scale	Product quality[b]	Label quality[c]	Detection
Professional	No	Large; frequently international	Very good	Excellent	Testing, side-by-side comparisons
Hack	No	Generally within a country or a limited region of a country	Poor	Good	Testing, physical examination
Minor petty	Yes?	Generally a few privately held stores	Very good	Good	Label examination
Major petty	Yes?	Generally a limited market segment in a given country	Excellent	Good	Label examination
Substitution	No	Generally a few privately held stores	Good	Good	Testing, examination

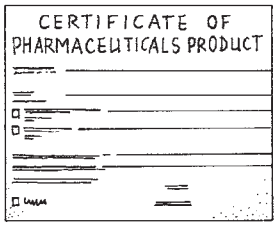
[a] In general, only the relabelers may have the correct product.
[b] Physical appearance, uniformity.
[c] Print quality, color.

Figure 19-3 Critical elements in quality assurance for pharmaceutical procurement

1. Product selection
- products with longer shelf life (for example, powders for reconstitution rather than oral suspensions)
- avoidance of products with bioavailability problems, when possible

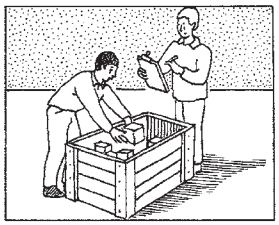


2. Product certification
- supplier prequalification
- recent GMP inspection reports from national drug authorities
- formal supplier-monitoring system
- limitation of purchases from new suppliers to noncritical products

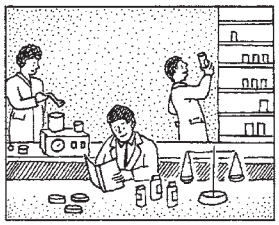


3. Product certification
- GMP certificate from drug regulatory authority (prequalification)
- certificate of pharmaceutical products (WHO-type) for all new products, new suppliers
- batch certificate (WHO-type) for problem drugs only

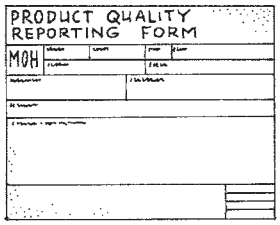
4. Contract specifications
- acceptable pharmacopeial standards
- language, labeling requirements
- minimum shelf life
- packaging standards



5. Inspection of shipments
- physical inspection of all shipments
- sampling for analysis of suspect products



6. Targeted laboratory testing
- therapeutically critical drugs
- drugs with known bioavailability problems
- new suppliers
- suppliers with quality difficulties in the past



7. Product problem reporting system
- system for reporting suspect or problem products

approached the design of its pharmaceutical quality assurance program.

Because resources are limited, countries should target priorities for quality assurance activities. The VEN (vital, essential, nonessential) method (Chapter 40) helps identify a small group of medicines that have the greatest health impact. Vital lifesaving medicines (antibiotics, cardiac medications, and intravenous solutions) warrant greater attention than other important but not lifesaving medications, such as analgesics. ABC analysis (Chapter 40) can be used to identify those medicines that have the greatest budgetary effect if their quality is unacceptable. The choice of medicines to monitor closely is based on the following criteria—

- Medicines with a narrow therapeutic window
- Medicines with inherent bioavailability problems
- Modified-release preparations
- Products from new suppliers and suppliers with problems in the past
- Medicines that require stable dosage forms and appearance

19.3 Obtaining good-quality pharmaceuticals

Obtaining medicines of good quality involves careful selection of suppliers and products, compliance with GMPs, reliance on appropriate pharmaceutical product or batch certificates, and detailed contract specifications.

Careful product selection

In many systems, therapeutic medicine formulary committees first assess the safety and efficacy of selected medicines on the basis of evidence from clinical trials (Chapter 16). Specific product selection involves assessing the technical documentation provided by the supplier on the pharmaceutical characteristics of the dosage form. Dosage forms that may offer longer shelf life include—

- Powders for reconstitution instead of injectable liquids
- Powders for reconstitution instead of oral suspensions
- Tablets instead of capsules

When appropriate, request and review product-specific stability studies from the manufacturer. For a few medicines, such as certain heart, asthma, and seizure medicines, studies that demonstrate bioequivalence among different manufacturers' products may also be necessary.

Select products with packaging that can withstand rough transport and extreme climatic conditions. Plastic containers may be better than glass bottles for intravenous solutions, oral liquids, and disinfectants. Avoid metal tins that will rust. In some countries, unit-of-use packages (blister

packs) and containers with smaller quantities (for example, 100 tablets rather than 1,000 tablets) may be cost-effective. These measures aim to avoid quality loss after the containers are opened or as a result of frequent handling. The increased costs should be weighed against the wastage and contamination that may occur with bulk containers, plus the costs of any repackaging.

Careful supplier selection

This step may be the most critical in quality assurance (see Chapter 21). Suppliers can be selected competitively by restricted tender with prequalification, through open tender with postaward qualification, or in some cases, through less formal procedures (see Chapters 18 and 21). Standard procedures should include requiring certifications, gathering information on supplier reliability and product quality, inspecting product samples, and if necessary, conducting laboratory testing of pharmaceuticals with high potential for bioavailability or stability problems. Country procurement offices obtained a major resource for helping assure quality pharmaceutical purchases when WHO launched its medicine prequalification program in 2001. Box 19-3 has more information on the program.

Contacts with DRAs and purchasing groups (for example, the United Nations Children's Fund and IDA Foundation)

Country Study 19-1
Building quality assessment infrastructure in Tanzania

Substandard pharmaceuticals circulating in the market are a problem in many countries. As part of a 2001 assessment, the Strategies for Enhancing Access to Medicines (SEAM) program took 110 samples of ten different medicines and found that 12.9 percent of the samples from public facilities and 13 percent from private pharmacies were substandard. A further measure of the quality of medicines in the marketplace is the percentage registered with the Tanzanian Food and Drugs Authority (TFDA). Only 26 percent of the medicines surveyed in the thirty-nine *duka la dawa baridi,* which are private drug shops, were registered, while a further 24 percent were notified. The quality of notified and unregistered medicines cannot be assured, since they have not passed through the registration process, which would include almost three-quarters of medicines sampled at the *duka la dawa baridi.*

SEAM collaborated with the TFDA to establish a comprehensive national quality assurance program that can ensure that both imported and locally manufactured pharmaceutical products meet approved quality standards. The main focus of the intervention was on product examination and testing at ports of entry and surveillance and testing of products circulating in the market. Market surveillance requires routine inspection of facilities and sampling of products in the marketplace, including distributors and retail outlets. This strategy required enhancing inspection and pharmaceutical testing capacity within the TFDA, which involved developing and incorporating a number of tools and activities, among them the following—

- Flow charts and standard operating procedures for structured inspection activities at ports of entry and facilities, such as warehouses, hospital dispensaries, retail pharmacies, and over-the-counter drug shops. The flow charts and procedures have been compiled into a *Level One Drug Inspectors' Handbook.*
- A thin-layer-chromatography-based program to screen pharmaceutical products (initially targeted at antimalarial medicines, then selected antibiotics and antiretrovirals).
- Quality assurance protocols and training materials based on a combination of visual inspection and non-laboratory-based testing (using thin-layer-chromatography Minilab). School of Pharmacy faculty at the Muhimbili University College for Health Sciences collaborated on the development and oversight of the inspectors' training.
- Support for TFDA inspectors' training, and monitoring and evaluation.
- Personal digital assistants to standardize the inspection process and allow computer downloads of inspection results for management review.

Working closely with stakeholders and sensitizing them to quality requirements helped get the quality assurance program established in 2002. Since then, improved efficiencies have resulted in a doubling of the number of pharmaceutical products screened and a quadrupling of the number of premises inspected—all with relatively few inspectors. The new quality assurance program has resulted in many product confiscations and importation refusals, in addition to closures of premises and improvements in standards. In summary, the quality assurance activities were conducted with relatively modest resources yet increased the presence of the TFDA in the marketplace, providing a significant deterrent to the marketing of substandard and counterfeit products.

Source: SEAM 2007.

Box 19-3
WHO's prequalification of medicines program

In 2001, WHO, in partnership with the United Nations Joint Programme on HIV/AIDS, the United Nations Children's Fund, and the United Nations Population Fund, and with support from the World Bank, launched its prequalification of medicines program to assess and approve manufacturers of medicines to treat HIV/AIDS, malaria, and tuberculosis. Since then, the program has added medicines and commodities related to reproductive health, and it also prequalifies quality-control laboratories. The program evaluates data on medicine safety, efficacy, and quality and inspects facilities for compliance with GMPs. Inspection activities have expanded to include manufacturers of selected APIs as well as clinical sites and contract research organizations. In addition, the program offers training workshops on how to meet prequalification requirements, assess multisource interchangeable medicines, and conduct and assess stability studies.

In 2009, the program prequalified 44 products, for a total of 237 products manufactured in sixteen countries (WHO 2010c). The program also prequalified three new quality-control laboratories to bring the total to eleven.

Originally intended for United Nations procurement agencies, the program has become a valuable resource for any purchaser, including countries themselves.

More information on the prequalification program is on WHO's website at http://apps.who.int/prequal/. The website lists all product and manufacturing site requirements, standards used in evaluating the product, and the profile of the inspection teams. It also includes the list of prequalified medicines and their manufacturers.

Source: WHO 2010c.

and product-quality testing laboratories can help with reference checks and exchanges of information on problem products. Publications by medicine information services and professional organizations, such as the U.S. Pharmacopeia, the FDA, and the American Society of Health-System Pharmacists, provide information on the bioequivalence of pharmaceuticals as well as on pharmaceutical recalls (see Annex 19-1).

A procurement office or agency needs to analyze information on suppliers' performance and develop and apply operational definitions and criteria to assess the reliability of suppliers and avoid subjectivity. Lack of explicit definitions and criteria provides rejected suppliers with the opportunity to question the integrity of the procurement process.

For products from new suppliers, visual inspection of samples of the product, packaging, and labeling is important. Some programs send samples for laboratory testing on a routine basis; others do so only when concerns arise about specific products. Although prepurchase testing may detect defective products, bear in mind that the samples are provided by the supplier, which will make every effort to ensure that the samples meet the standards. The samples may not, however, be representative of what is actually delivered.

Chapter 21 discusses the need for an information system that provides the procurement office and tender committee with feedback on suppliers' compliance with contracts. Keeping a record of condition of received goods, compliance with contract terms, and timeliness of delivery is essential. This information, and that from the adverse drug reaction and product-quality reporting system, should be considered when assessing offers and awarding supply contracts.

Product certification

WHO has established GMPs for pharmaceutical products, similar to those enforced by the national pharmaceutical control agencies in industrialized countries. They include criteria for personnel, facilities, equipment, materials, manufacturing operations, labeling, packaging, quality control, and in most cases, stability testing.

In countries with effective pharmaceutical control agencies, adherence to GMPs is enforced by a system of inspections and regulatory controls, often specific to individual medicine dosage forms. A manufacturer may have acceptable standards for solid dosage forms but not for sterile injectable preparations. Recent reports of GMP inspections and pharmaceutical recall histories can be obtained by writing to national pharmaceutical control agencies. Often, a supplier must approve or at least expedite requests for performance reports from national pharmaceutical control agencies, and failure to obtain such reports for the buyer makes past performance suspect.

Buyers with pharmaceutical staff trained in GMP inspection may perform their own inspections of local manufacturers that are potential suppliers, if funds are available to do so.

Countries that participate in the scheme agree to certify that pharmaceuticals are registered in the exporting country

and that manufacturers' facilities have been inspected and comply with GMPs. However, a WHO study (1995) showed that very few importing countries actually request pharmaceutical product certificates for registration or procurement purposes.

This certification scheme provides some assurance, based on inspection of the manufacturing facilities for GMPs by the competent authority of the exporting country. For the procurement office, it is an inexpensive means to help ensure the quality of purchased products. Through the certification scheme, the procurement office should be able to obtain the following information—

- Whether a product is legally marketed in the exporting country, and if not, the reasons why
- Whether the supplier manufactures the dosage forms, packages, and/or labels a finished dosage form manufactured by an independent company, or is involved in none of these activities
- Whether the manufacturer of the product has been inspected and the periodicity of inspection
- Whether the certificate is provisional, pending technical review
- Whether the information submitted by the supplier satisfies the certifying authority on all aspects of manufacture of the product undertaken by another party

The reliability of the pharmaceutical product certificates issued under the WHO scheme and access to them depend largely on the—

- Reliability and responsiveness of the exporting country's authority
- Capability of the exporting country's authority to make adequate GMP inspections
- Capability of the importing country's authority to assess the authenticity or validity of the certificate of a pharmaceutical product submitted, especially when it is submitted through the manufacturer or importing agent

Therefore, product certification under the WHO scheme is only as reliable as the agency performing it, and WHO estimates that only about 20 percent of member countries have a national drug regulatory system that can ensure the quality of medicines circulating in their national markets (WHO 2008b). For this reason, certificates should be accepted with caution unless the national DRA's competence to fulfill the scheme is known. In addition, although national pharmaceutical-control agencies in the major pharmaceutical-exporting countries are generally conscientious in their assessments, receiving reports may take some time. Agencies in some countries have been found to be less reliable and responsive.

WHO recognizes that today's pharmaceutical manufacturing sector looks much different from when the scheme was formulated decades ago under the assumption that a pharmaceutical product would be sold directly from the country of manufacture to the country of final destination. Pharmaceutical manufacturing and trade have become far more globalized in that different stages of manufacturing take place in different countries before the product reaches the final destination. Because of this evolution and other identified problems, WHO has proposed revising the scheme (WHO 2008b).

Product pedigrees

The purpose of a pharmaceutical pedigree is to establish a chain of custody from the manufacturer to the dispenser by documenting all parties that have handled a particular unit of a pharmaceutical as it travels through each step in the supply chain. Pharmaceutical wholesalers who provide fraudulent or no product pedigrees may help divert counterfeits into legitimate distribution systems. Failure to comply with the pedigree requirements is against the law in the United States.

Implementing a pharmaceutical pedigree process can be done with paper or electronic records. For example, affixing radio frequency identification (RFID) or bar codes to packaging would help maintain supply chain integrity and improve inventory control (see Section 19.4). Although electronic tracking is likely more efficient and secure, it requires expensive technology and training. Paper-based systems may be executed quickly but in the long run may be more time-consuming and more susceptible to forgery.

Batch certificates

Reliable pharmaceutical manufacturers may comply with GMPs by routinely conducting batch analyses. Local manufacturers that do not have their own quality-control laboratories may contract quality-control testing services from other manufacturers, private testing facilities, or national reference laboratories.

Some pharmaceutical procurement offices request other certificates, such as the certificate of free sale, the certificate of origin, or the certificate of licensing status (see Table 19-3). These certificates do not provide important information regarding compliance with GMPs, or results of laboratory testing of samples from individual batches. For this reason, the WHO-type certificate of a pharmaceutical product and batch certificate are preferred.

DRAs and the procurement market today

In many countries, DRAs and procurement offices do not work together effectively, nor are integrated information

Table 19-3 Comparison of certificates used in pharmaceutical procurement

Type of certificate	Uses	Limitations
WHO-type certificates		
Certificate of pharmaceutical product		
• Issued by DRA in exporting country • Provides licensure status of product • Provides inspection status of manufacturer	• Essential for product licensure • Ideally required for all new products • Prequalification of suppliers • Screening of new suppliers	• Is only as reliable as issuing DRA • Does not provide batch-specific information
Statement of licensing status		
• Issued by DRA in exporting country • States that product is licensed	• Prequalification of suppliers • Screening of new suppliers	• Does not provide batch-specific information
Batch certificate		
• Issued by manufacturer or DRA in exporting country • Confirms that individual batches conform to specifications • Linked to certificate of pharmaceutical product	• Usually requested for antibiotics • May be required for problem medicines	• Issued by few DRAs • Easily falsified • Many require additional expense
Non-WHO-type certificates		
Free-sale certificate		
• Issued by DRA in exporting country • Confirms product is sold in the country of origin	• Commonly used for licensure	• No indication that product has been evaluated for safety and efficacy • No indication that product is registered for use in country of origin
GMP certificate		
• Issued by DRA in exporting country	• Prequalification of suppliers	• Only as reliable as issuing DRA
Analytic batch certificate		
• Issued by manufacturer • Contains results of analytical tests • Not linked to certificate of pharmaceutical product	• Postqualification of suppliers	• Manufacturers' certificates may be falsified • Does not necessarily conform to specifications approved at time of product licensure

systems in place. Ideally, when a DRA exists and the medicine registration system is operational, procurement by government agencies should be limited to medicines registered by the DRA. Procurement offices should seek information from the DRA and strive for closer cooperation with the authority. To facilitate registration of generic medicines, the evaluation and approval process should not be complicated. Clinical trial data, except for bioequivalence data, are not normally required, allowing the submission of an abbreviated application by the manufacturer or distributor. WHO recommends that all medicines on the public or private market in a country, whether they are imported or locally manufactured, be subject to the same standard of control, including medicine registration.

The standard of control varies from country to country. In some exporting countries, medicines are registered and freely sold but not rigorously evaluated for efficacy. In other countries, which do evaluate efficacy, certain medicines may have been registered before evidence of efficacy was legally required. Moreover, in some countries, manufacturers may produce exclusively for export; the exporting country's DRA may not closely scrutinize these manufacturing plants. Procurement offices still need to request certificates from the DRA of the exporting country, as recommended by WHO.

Contract specifications

Detailed specifications to help ensure that high-quality products are bought and received include the following—

- Analytical methods and source of reference materials or documented evidence of suitability for the material used to assess product-quality attributes and certificate of analysis.
- Portions of manufacturers' reference materials to be used in product-quality assessments. For these reference materials, the manufacturers will supply either the API used in the manufacture of the product or a purified portion of the API. Because the reference material is used to assign qualitative and quantitative properties, its identity must be assured and its

purity must be suitable to perform the assessments at an appropriate confidence level for the intended use of the material. The identity of a reference material is generally assessed by infrared spectral comparisons and quantitative assessments performed by ultraviolet-visible spectral measures, either directly or in conjunction with chromatographic procedures. However, for most pharmaceutical measurements, the identity and quality of solid materials can be assessed by melting point/mixed melting point measurements, while liquids can be assessed by refractive index measurements.

- Language for the product label and package insert, which should be the language or languages common to the country.
- Minimum information required on the label (generic or International Nonproprietary Name, dosage form, strength, quantity, expiration date, manufacturer, batch number).
- Additional information, such as the product registration number and date of manufacture.
- Standards for packaging that will withstand the specific storage and transport conditions (for example, corrugated boxes with specifications for dividers, maximum size, and maximum weight).

To reduce theft and resale, some programs may require labeling and logos to indicate that the product is solely for distribution within a particular health care program (for example, ministry of health, social security fund).

Contract specifications are discussed in detail in Chapter 39.

19.4 Verifying the quality of shipped products

The quality of products received should be verified as soon as possible by physically inspecting each shipment and testing selected products in the laboratory as required by regulation. In addition, more advanced product-tracking technologies have been introduced to help ensure the integrity of the pharmaceutical supply chain.

Product identification technology

The traditional approach to assuring product integrity is labeling with batch number and expiration date. Unfortunately, this labeling is easily duplicated. To make fraud more difficult, several approaches are available that use overt or covert systems. *Overt technologies* are visible to the eye, and *covert technologies* require devices for detection. Because each step up in identification technology costs more, the most advanced technologies are used on high-value products or in large-quantity inventory control.

Bar coding: The simplest and least expensive technology for product tracking is the bar code, which has been adopted widely in many industries. Its uses range from tracking shipping containers to individual dosage units. The airline industry makes extensive use of this technology to track and direct baggage, and the retail industry has made bar coding the standard to track inventory and sales. Because of their widespread use and simplicity, bar-code detecting devices are relatively inexpensive.

Radiofrequency identification: The RFID tag is a radiofrequency transponder chip with a permanent unique identification code and the ability to be programmed with product information, such as batch number and expiration date. The combination of product information and identification code provides a high level of security against counterfeiting. RFID can be used overtly or covertly—either visible on the product or hidden in the packaging. Another advantage of the RFID technology is the ability to detect several different items at the same time, unlike visual bar-code readers, which must have each tag visible and separate for reading. However, until this RFID technology matures and becomes more widespread, it will remain much more expensive than the traditional bar-code technology.

Holograms: Hologram technology provides visual authentication that can be very difficult to counterfeit or remove (although instances of fake holograms have been found on counterfeit antimalarial products in Southeast Asia). However, the technology is not easily automated and optimally requires an authentic label or accurate image for visual comparison.

Other technologies that have been developed for product authentication include color-shifting inks, ultraviolet printing, and embedded chemical markers and infrared tags. As the technologies mature, several will likely be used to assure different aspects of the supply chain. The continuing adoption of these authentication technologies will make product counterfeiting more difficult and expensive, but unfortunately will not likely eliminate it.

Inspection of shipments

Regardless of other quality assurance procedures in use, each pharmaceutical shipment should be physically inspected. This means verifying adherence to contract specifications and order completeness as well as inspecting samples of all items to spot any major problems. Training competent receiving staff can be an economical means of ensuring pharmaceutical quality and reducing losses from supplier negligence or fraud.

Inspection in the exporting country before shipment can be arranged through an independent agency (for

example, the Société Générale de Surveillance), for early detection of noncompliance with contract terms or defective products.

Tiered pharmaceutical quality assessments

As mentioned earlier in the chapter, the safety and efficacy of an API is the most critical attribute of a pharmaceutical product. The safety and efficacy of new APIs in the European Union, Japan, and the United States are determined in accordance with exhaustive ICH consensus guidelines that have been incorporated into the laws and regulations of those sovereign areas.

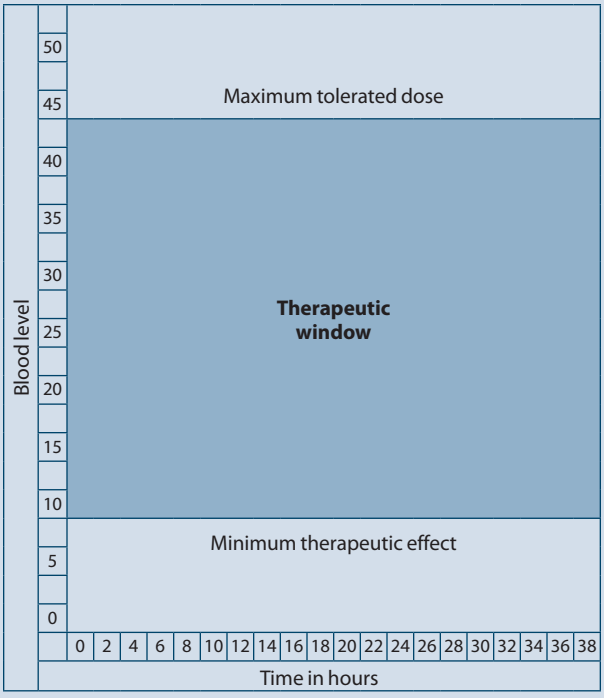
When the safety and efficacy of an API have been established, the dosage regimen is set so the minimum therapeutic level is attained without exceeding the maximum tolerated dose. That level of efficacy is called the "therapeutic window" (see Box 19-4). Pharmaceutical quality assessments may include bioavailability testing to ensure that the API falls within the therapeutic window.

Three tiers of product-quality assessment differ by cost and levels of precision, accuracy, and sensitivity—

1. *Minilab® screening assessments:* The Global Pharma Health Fund developed the Minilab to rapidly assess whether products are grossly substandard and to detect counterfeit products with no API or the wrong ingredients (see http://www.gphf.org/web/en/minilab for more information). The Minilab uses a thin-layer-chromatography method that does not require standard laboratory resources, so it can be used in the field, such as at ports of entry, while providing a good level of quality assurance. The Minilab has methods available for more than fifty pharmaceutical products and is regularly incorporating more.
2. *Validated laboratory assessments or legal reference method assessments:* These methods are used to assess assays, content uniformity, known impurities, and API dosage release. For medicines with a narrow therapeutic index, such as warfarin sodium, or for pharmaceuticals that fail the first-tier screening assessment, more accurate laboratory assessment technologies are required to support litigation concerning quality standards violations. Legal reference methods are methods of analysis that have been adopted into law and are suitable for use in litigation; however, Minilab screening and validated assessments are generally quicker, less labor intensive, and less expensive than legal reference methods, which are the gold standard.
3. *Specialized instruments:* Methods such as high-performance liquid chromatography coupled with

Box 19-4
Therapeutic window

Fortunately, the overwhelming majority of pharmaceutical products have a large therapeutic window, which is a great advantage for manufacturers and consumers. A wide therapeutic window allows the production of fewer dosage levels, which reduces production, supply, and inventory costs and allows consumers to more easily take a dose of a medicine that is efficacious and well tolerated. Products with a narrow therapeutic window require strict monitoring of the patient's therapeutic response; for example, patients taking the anticoagulant warfarin sodium must have their individual coagulation times strictly monitored to determine the ideal dose. A further indicator of the critical dosing requirement for this product is the large number of tablets available containing 1, 2, 2.5, 3, 4, 5, 6, 7.5, or 10 mg. These dosing levels contrast markedly with those of acetaminophen (paracetamol), which has a wide therapeutic window. In the United States, acetaminophen is often marketed as a 325-mg dosage unit, whereas in Europe the dosage unit generally is 500 mg. The dosing instructions for both products instruct the user to take one or two units up to four times per day.



mass spectrometry may be used to determine unknown impurities and metabolites. Generally, these technologies are expensive and require highly trained individuals to operate them and interpret the data.

In summary, wide-therapeutic-index products may be screened rapidly to assess their quality clearance with minimal risk of compromising their safety and efficacy. Narrow-therapeutic-index products and those that fail the rapid screening technologies should be assessed by validated technologies that are fast and efficient. Products that fail the validated technologies may require further assessments by the legal reference methods of the sovereign state to support litigation or with specialized instrumentation to litigate untoward or unexpected contamination.

Laboratory testing

Upon arrival after shipment, batch samples may be laboratory tested routinely or "by exception." Most programs test selected samples from only some of the batches. Testing by exception means that analyses are done only when a supplier or a particular product is suspect.

Laboratory testing is costly in terms of technical human resources, equipment, and reagents. Guidelines should target sampling to products that (a) have the greatest potential for bioavailability and stability problems, (b) are from new or questionable suppliers, and (c) have been the source of complaints. With new suppliers, a probationary testing period—for example, testing the first three shipments, then shifting to intermittent sampling—is useful. Suppliers whose failure rates are unacceptable are dropped from future tenders. Sampling from well-established suppliers is done much less frequently, often only for at-risk products.

Programs that require routine testing of samples for all products prior to distribution to health facilities often produce significant delays in product availability at the health-facility level. The need for laboratory testing of products reported to have problems should be carefully assessed; many problems with quality are detectable on visual inspection and do not require laboratory testing. For example, verified observations of tablets that crumble before their expiry date, oral suspensions that harden, or injectable solutions that contain particles are enough to justify recalling the product without testing.

The tests that should be performed depend on the pharmaceutical and the reason for testing. Basic chemical analyses are done to verify the identity of the medicine and under extenuating circumstances to look for degradation, chemical contamination, or adulteration. WHO advocates a system of economical, less technically demanding basic tests for commonly used medicines (WHO 1998) that can be done in simple laboratories. A complete analysis of tablet and capsule forms includes tests for identity, strength or potency, uniformity, impurities, disintegration, and dissolution.

Biological testing is more specialized and can be performed only in established facilities with staff trained to use microbiological and pharmacological methods. Microbiological tests include sterility tests for injectable medicines and eye preparations and microbiological assays of antibiotics and vitamins. Pharmacological tests include the pyrogen test; toxicity tests; hormone assays, such as for insulin and pituitary derivatives; and tests to determine the bioavailability of selected pharmaceuticals.

Construction of a quality-control laboratory where one does not already exist should be considered with caution. It may not be cost-effective for some countries to establish a sophisticated national pharmaceutical control laboratory for a number of reasons, including—

- Low projected volume of work
- Insufficient financial resources for land purchase, facility construction, testing equipment, furniture, supplies, equipment maintenance, salaries, training, and other operating costs
- Lack of trained personnel, such as microbiologists, pharmacologists, laboratory technicians, and animal caretakers
- Lack of local capacity for maintenance and repair of equipment, difficulty in obtaining spare parts, irregular and unstable power supply

In some countries, a college of pharmacy or an independent laboratory may have some of the required testing facilities. Also, many international quality-control laboratories provide pharmaceutical analyses at a relatively reasonable price. If analyses are performed by foreign laboratories, foreign exchange and billing problems may be reduced by requiring the suppliers to pay the laboratory directly, with the arrangement clearly described in the purchase contract. In addition, chain-of-custody and legal standing of the testing laboratory in the importing country may be at issue.

19.5 Maintaining pharmaceutical quality

Maintaining medicine quality requires careful attention to storage conditions and transport, as well as to dispensing practices and use.

Appropriate storage and transport

Procedures to help maintain pharmaceutical quality begin with proper storage conditions at the port and prompt release. Storage activities are discussed in Chapters 42, 44,

and 46, and proper transport conditions are addressed in Chapter 25.

Appropriate dispensing and use

Inappropriate dispensing procedures contribute to pharmaceutical product deterioration and contamination or medication errors. The following procedures help maintain the quality of pharmaceutical products—

- Use only proper dispensing containers (for example, airtight containers, light-resistant bags or vials); the paper envelopes often used for end-user dispensing do not protect tablets and capsules.
- Require clear labeling of dispensed medicines, and enforce procedures to label products with the patient's name, the medicine's name, its strength, its expiration date, and instructions for its use and storage.
- Write information and instructions in the local language, avoiding the use of abbreviations, or use symbolic instructions.

The prescriber and the dispenser should counsel the patient on the proper use of medications, explaining *what* the medicine is, *why* the patient needs it, *how* to take it, and *where* and *how* to store it until treatment is completed, in addition to possible contraindications and adverse reactions (see Chapter 30).

Pharmaceutical product presentations: treatment kits, co-packaging, and fixed-dose combinations

Medicines can be packaged according to therapeutic regimens or for delivery to dispensing sites or individual patients to facilitate and reduce the costs of inventory management and distribution systems. For example, a tuberculosis treatment kit could include enough antimicrobial products for a particular number of patients. Broader-based treatment kits for poorly served areas may include a selection of essential medicines that supplements the national supply system (see Chapter 26 for more information).

Co-packaging or co-blistering is a method commonly used to deliver multiple medicines for a specific treatment regimen such as tuberculosis. These packages are prepared from individual pharmaceutical products, so their quality assessments should be based on each product's individual standards, including stability testing.

Fixed-dose combination (FDC) products have more than one active ingredient formulated into one product—for example, the anti-tuberculosis medicines isoniazid and rifampin are available as single products or as an FDC in one pill. FDCs simplify the prescription of medicines and the management of pharmaceutical supply, improve patient adherence, and may also limit the risk of treatment-resistant infections caused by inappropriate medicine selection and monotherapy, as is the case with artemisinin-based combination therapies. WHO recommends FDCs be developed for antiretroviral pharmaceutical products to simplify HIV/AIDS treatment regimens and to improve patient adherence. From a regulatory standpoint, FDCs are treated as new pharmaceutical entities in which the individual APIs must be shown to be stable and bioavailable in this composite product (WHO 2003).

19.6 Monitoring pharmaceutical quality

Despite every effort, defective products occasionally slip through, and the quality of even the best-manufactured product may deteriorate. Furthermore, health care personnel and patients alike may have erroneous perceptions that only brand-name products from innovator firms are of good product quality, especially when generic products are not well known and accepted.

Product problem reporting system

Establishing a national product problem reporting system is important so that health workers can report suspected or confirmed problems with specific pharmaceutical products. Product problem reporting should be part of an overall pharmacovigilance system, which also includes monitoring and reporting adverse drug events and medication errors. Chapter 35 covers those areas of pharmacovigilance in detail.

Figure 19-4 is a sample medicine and supplier evaluation form that pharmacy staff and health care providers at all levels can use to report suspected lapses in pharmaceutical or packaging quality. Standard procedures for product problem reporting should specify—

- Who should report the perceived product quality problem
- How to fill in the reporting form
- Where and to whom the reporting form should be sent
- What additional measures need to be taken, such as sending samples or information concerning the quantities involved
- What follow-up information should be provided to the person or facility that reported the problem

Quality assurance program staff should carefully analyze all reports, using laboratory testing as required, and take appropriate actions. The reporter should be informed about the results and the actions taken, even if products are

Figure 19-4 Sample medicine and supplier evaluation form

Organization of Eastern Caribbean States
Eastern Caribbean Drug Service

Submitted by: _____

Country: _____ Date: _____

Sample Location:
☐ CMS
☐ Other _____
(specify)

MEDICINE AND SUPPLIER EVALUATION FORM

Address communications to:

ECDS
PO Box 3093
La Clery
Castries
St. Lucia
Telephone: (809-45) 25058/25895

Medicine Description: Generic Name, Strength, Form,	Brand Name	Medicine or Supplier	Lot Number or Batch Number	Expiration Date	Comments

Suggested criteria for medicine evaluation:

1. Physical characteristics • e.g., hardness, color, mixing ease for reconstitution
2. Packaging • expiry date, lot or batch number, package insert
3. Labeling • language (English vs. French), legibility (especially ampoules)
4. Patient acceptability • taste, color, size of tablet, etc.
5. Health care provider acceptability • e.g., is the ampoule easy to break?

Guidelines for medicine sampling:

1. Take samples from previously unopened containers.
2. Minimum sample size: tablets/capsules—200; injections—40 ampoules; liquids—40 mL.
3. Tablets/capsules must be tightly packed in plastic/glass vial (DO NOT USE PAPER OR PLASTIC ENVELOPES).
4. Enclose COMPLETE LABEL (generic name, strength, quantity, manufacturer and supplier names, lot/batch number, expiry date, date of manufacture).
5. Print label legibly, and double check lot number for accuracy.

not defective, to encourage continued participation in the program. Product problem reports and results should be recorded to provide information for future procurement.

Product recalls

Pharmaceutical products found to be defective should be recalled quickly. The quality assurance unit in the country's DRA should develop standard procedures for carrying out the recall. Rapid action helps avoid unnecessary exposure once the problem has been detected. The central distributor's inventory control system should include information on all batches that have been received. Because tracking individual batches to the health facility is often either impractical or fraught with uncertainty, recall notices have to be sent to all health facilities that received any of the products in question to check their shelves and return the products to the central distribution point.

Recalls may be classified according to the degree of risk to the consumer: (a) serious illness or death, (b) temporary or mild illness, or (c) no adverse clinical effect. The level of recall is determined by both the degree of risk and the extent of distribution of the product and may be directed at the patient, the health facility, or the medical stores level.

After issuing a recall, the quality assurance program should monitor its progress to ensure complete compliance. The supplier should be notified and required to replace defective products. The procurement office should pursue other remedies specified in the contract, such as withholding payment or obtaining reimbursement for or replacement of the defective products.

19.7 Personnel and training in the supply system

Central to the operation of most well-run pharmaceutical supply systems is at least one qualified pharmacist with some training or experience in industrial pharmacy and procurement. Such an individual can be invaluable in establishing and overseeing quality-control practices suited to local requirements. This person should participate in—

- Selecting medicines
- Setting technical specifications for pharmaceutical contracts
- Reviewing supply offers and selecting suppliers
- Reviewing storage and transportation facilities
- Coordinating any pharmaceutical quality testing and helping to train the inspectors who check pharmaceutical shipments

In some government systems, qualified pharmacists are employed at all levels, including the district hospitals, and they are expected to oversee local storage and transportation conditions. In addition, they report problems or questions concerning individual medicines to the main office. In other countries, locally trained dispensers are responsible for much of the day-to-day work and must be trained to detect and report quality problems. Some countries must rely on staff that has not received any technical training in pharmaceutical management.

In addition to pharmacists and pharmaceutical assistants, other staff members involved in quality assurance need training and supervision as a part of quality assurance efforts.

- Physicians, health administrators, and health system officials must know about the factors that influence pharmaceutical quality to make informed decisions about supply sources and to monitor and promote quality assurance in their facilities.
- Port-clearing personnel should be trained to identify the categories of pharmaceuticals requiring special storage and transport conditions.
- Clerks responsible for inspecting pharmaceutical shipments should receive formal training in inspection procedures.
- Pharmaceutical inspectors must be familiar enough with pharmaceutical labeling and packaging materials to determine whether contract conditions regarding pharmaceutical dosage, packaging, and labeling have been met.
- Staff involved with local repackaging should be trained to ensure pharmaceutical quality and to follow good practices, especially regarding label control.
- Physicians, nurses, and paramedical personnel handling pharmaceuticals throughout the health system need to know about the factors that influence pharmaceutical quality and what they can do to ensure that the medicines dispensed to patients are safe and effective.

Quality assurance is a widely shared responsibility. Within a supply system, the organizational structure needs to establish the responsibilities for the review and preservation of pharmaceutical quality at all levels. If a pharmaceutical becomes ineffective or unsafe by the time it reaches the patient, then all the other activities of the supply system have been in vain. ■

ASSESSMENT GUIDE

Quality assurance structures

- Are there stated policies and practices aimed at ensuring pharmaceutical quality?
- Who is responsible for monitoring pharmaceutical quality?
- In what laboratories is quality-control testing done?
- Does a formal system exist for reporting product quality complaints?

Quality assurance procedures

- Is the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce used systematically?
- Are favorable GMP inspections required for all suppliers, including local manufacturers?
- Is a physical inspection made of all pharmaceuticals received?
- Are all pertinent documents and labeling, including patient inserts, reviewed for accuracy and compliance with standards?
- How many laboratory analyses were performed during the past year of the total number of products or batches procured?
- To whom are results of analyses of suspected or confirmed defective products communicated?
- Are the test results of substandard medicines recorded for use in future procurement assessments?
- Is information on pharmaceutical stability and problem pharmaceuticals used in evaluating suppliers and pharmaceutical products?
- Are storage conditions periodically evaluated at the ports of entry? At the central warehouse? At district and regional stores? In hospital pharmacies? At health centers and rural health posts?
- Are transport conditions maintained to ensure product quality?
- Are good dispensing practices followed in the health facilities or pharmacies?
- Are the various levels of health workers adequately trained to carry out their respective roles in quality assurance?

Outcome of quality assurance

- In the previous year, how many reports were submitted on pharmaceutical product problems?
- What number of pharmaceuticals or batches failed quality-control testing of the total number of pharmaceuticals or batches tested in the previous year?

References and further readings

★ = Key readings.

Ahmad, K. 2004. Antidepressants Are Sold as Antiretrovirals in DR Congo. *Lancet* 363:713.

Bogdanich, W. 2007. "Chinese Chemicals Flow Unchecked onto World Drug Market." *New York Times,* October 31. <http://www.nytimes.com/2007/10/31/world/asia/31chemical.html>

CPM (Center for Pharmaceutical Management). 2003a. *Access to Essential Medicines: Cambodia, 2001.* Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, Va.: Management Sciences for Health.

———. 2003b. *Access to Essential Medicines: El Salvador, 2001.* Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, Va.: Management Sciences for Health.

———. 2003c. *Access to Essential Medicines: Ghana, 2001.* Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, Va.: Management Sciences for Health.

———. 2003d. *Access to Essential Medicines: Minas Gerais, Brazil, 2001.* Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, Va.: Management Sciences for Health.

———. 2003e. *Access to Essential Medicines: Rajasthan, India, 2001.* Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, Va.: Management Sciences for Health.

———. 2003f. *Access to Essential Medicines: Tanzania, 2001.* Prepared for the Strategies for Enhancing Access to Medicines Program. Arlington, Va.: Management Sciences for Health.

CPM/MSH (Center for Pharmaceutical Management/Management Sciences for Health). 2011. *Center for Pharmaceutical Management: Technical Frameworks, Approaches, and Results.* Arlington, Va.: CPM.

FDA (U.S. Food and Drug Administration). 2010. Office of International Programs website. <http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofInternationalPrograms/default.htm>

———. 2007. "FDA Warns Consumers about Counterfeit Drugs from Multiple Internet Sellers." FDA news release P07-76, May 1. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108904.htm>

Gammon, D. L., S. Su, J. Jordan, R. Patterson, P. J. Finley, C. Lowe, and R. Huckfeldt. 2008. Alteration in Prehospital Drug Concentration after Thermal Exposure. *American Journal of Emergency Medicine* 26(5):566–73.

Hogerzeil, H. V., G. J. A. Walker, and M. J. de Goeje. 1993. *Stability of Injectable Oxytocics in Tropical Climates: Results of Field Surveys and Simulation Studies on Ergometrine, Methylergometrine and Oxytocin*. Geneva: World Health Organization.

Hogerzeil, H. V., A. Battersby, V. Srdanovic, and N. E. Stjernstrom. 1992. Stability of Essential Drugs during Shipment to the Tropics. *British Medical Journal* 304:210–2.

Hogerzeil, H. V., A. Battersby, V. Srdanovic, L. V. Hansen, O. Boye, B. Lindren, G. Everitt, and N. E. Stjernstrom. 1991. *WHO/UNICEF Study on the Stability of Drugs during International Transport*. Geneva: WHO/UNICEF. <http://whqlibdoc.who.int/hq/1991/WHO_DAP_91.1.pdf>

Hussain, K., P. Ibrahim, Z. Ismail, M. T. Majeed, and A. Sadikun. 2009. Traditional and Complementary Medicines: Quality Assessment

Annex 19-1 Resource organizations

Crown Agents
St. Nicholas House
St. Nicholas Road
Sutton, Surrey SM1 1EL
United Kingdom
http://www.crownagents.com

European Directorate for the Quality of Medicines (EDQM)
European Pharmacopoeia
7, Allée Kastner, CS 30026
F67081 Strasbourg
France
http://www.pheur.org

European Free Trade Association (EFTA)
9–11, Rue de Varembé
CH 1211 Geneva 20
Switzerland
http://secretariat.efta.int

European Medicines Agency (EMA)
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom
http://www.ema.europa.eu

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
15, Chemin Louis-Dunant
P.O. Box 195
CH 1211 Geneva 20
Switzerland
http://www.ich.org

IDA Foundation
Slochterweg 35
1027 AA Amsterdam
P.O. Box 37098
1030 AB Amsterdam
The Netherlands
http://www.idafoundation.org

U.S. Food and Drug Administration (FDA)
Many of FDA's materials are available on its website: http://www.fda.gov. Specific categories of information are available—

- CDERLearn at http://www.fda.gov/cder/learn/CDERLearn/default.htm is the site with educational tutorials.
- The Orange Book lists U.S.-approved medicines and their therapeutic equivalence. It is available at http://www.fda.gov/cder/ob/default.htm.
- Drugs@FDA at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ presents approval data and labeling information.
- The FDA Office of Regulatory Affairs at http://www.fda.gov/ora has publications and training materials available on inspection, compliance, and laboratory operations.
- The FDA Office of International Programs at http://www.fda.gov/InternationalPrograms/default.htm describes FDA's activities in other countries.

World Health Organization
Essential Medicines and Pharmaceutical Policies Department
Avenue Appia 20
CH 1211 Geneva 27
Switzerland
http://www.who.int/medicines/en

Strategies and Safe Usage. *Southern Med Review* 2(1):19–23. <http://apps.who.int/medicinedocs/documents/s16460e/s16460e.pdf>

ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). 2003. *ICH Harmonised Tripartite Guideline Stability Testing of New Drug Substances and Products Q1A(R2) (Second Revision): Current Step 4 Version.* 6 February. Geneva: ICH. <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2__Guideline.pdf>

———. 2000. *ICH Harmonised Tripartite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7: Current Step 4 Version.* 10 November. Geneva: ICH. <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf>

Kasim, N. A., M. Whitehouse, C. Ramachandran, M. Bermejo, H. Lennerna, A. S. Hussain, H. E. Junginger, et al. 2004. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. *Molecular Pharmaceutics* 1(1):85–96.

Newton, P. N., F. M. Fernández, A. Plançon, D. C. Mildenhall, M. D. Green, L. Ziyong, E. M. Christophel, et al. 2008. A Collaborative Epidemiological Investigation into the Criminal Fake Artesunate Trade in South East Asia. *PLoS Medicine* 5(2):e32.

Pau, A. K., N. K. Moodley, D. T. Holland, H. Fomundam, G. U. Matchaba, and E. V. Capparelli. 2005. Instability of Lopinavir/Ritonavir Capsules at Ambient Temperatures in Sub-Saharan Africa: Relevance to WHO Antiretroviral Guidelines. *AIDS* 19(11):1233–4.

Promoting the Quality of Medicines Program. 2010. *Matrix of Medicine Quality Reports Affecting USAID-Assisted Countries.* (Updated regularly.) Rockville, Md.: United States Pharmacopeial Convention. <http://www.usp.org/pdf/EN/dqi/ghcDrugQualityMatrix.pdf>

SEAM (Strategies for Enhancing Access to Medicines). 2007. *Tanzania: Product Quality Assurance Program*. Arlington, Va.: Management Sciences for Health. <http://www.msh.org/seam/reports/SEAM_TANZANIA_Quality_Assurance.pdf>

Seiter, A. 2005a. *Pharmaceuticals: Counterfeits, Substandard Drugs and Drug Diversion.* HNP Brief #2. Washington, D.C.: World Bank. <http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1109774792596/HNPBrief_6.pdf>

———. 2005b. *Pharmaceuticals: Quality Assurance in the Distribution Chain*. Washington, D.C.: World Bank. <http://apps.who.int/medicinedocs/documents/s16759e/s16759e.pdf>

USP (United States Pharmacopeia). No date. *US Pharmacopeia–National Formulary.* Updated annually. Rockville, Md.: United States Pharmacopeial Convention. <http://www.usp.org/USPNF/>

———. 2007. *Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide*. Rockville, Md.: United States Pharmacopeial Convention. <http://www.usp.org/pdf/EN/dqi/ensuringQualityOperationalGuide.pdf>

USP and USAID (U.S. Pharmacopeia and U.S. Agency for International Development). 2009. *Survey of the Quality of Selected Antimalarial*

Medicines Circulating in Madagascar, Senegal, and Uganda. Rockville, Md.: United States Pharmacopeial Convention. <http://www.usaid.gov/our_work/global_health/hs/publications/qamsa_report_1109.pdf>

WHO (World Health Organization). 2010a. *Guidelines for Implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*. <http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html>

———. 2010b. *Medicines: Counterfeit Medicines*. Fact sheet 275. Geneva: WHO. <http://www.who.int/mediacentre/factsheets/fs275/en/index.html>

———. 2010c. Prequalification of Medicines Success in 2009. *WHO Drug Information* 24(1):3–6. <http://www.who.int/medicines/publications/druginformation/DrugInfo2010_Vol24-1.pdf>

———. 2010d. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 44th Report. Geneva: WHO. <http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf>

———. 2009a. Prequalification of Quality Control Laboratories. *WHO Drug Information* 23(4):300–5. <http://whqlibdoc.who.int/druginfo/23_4_2009.pdf>

———. 2009b. Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. Annex 2 to *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 43rd Report. Geneva: WHO. <http://apps.who.int/medicinedocs/documents/s16236e/s16236e.pdf>

———. 2008a. *The International Pharmacopoeia.* 4th ed. Geneva: WHO. <http://www.who.int/medicines/publications/pharmacopoeia/overview/en/>

———. 2008b. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. *WHO Drug Information* 22(3):211–9. <http://whqlibdoc.who.int/druginfo/22_3_2008.pdf>

———. 2007a. General Guidelines for the Establishment, Maintenance and Distribution of Chemical Reference Substances. Revision. Annex 3 to *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 41st Report. Geneva: WHO. <http://apps.who.int/medicinedocs/documents/s14139e/s14139e.pdf>

———. 2007b. *Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials.* Good Manufacturing Practices and Inspection, 2nd updated ed. Vol. 2. Geneva: WHO. <http://apps.who.int/medicinedocs/documents/s14136e/s14136e.pdf>

———. 2004a. Stability Testing for Hot and Humid Climates. *WHO Drug Information* 18(2):113–6. <http://whqlibdoc.who.int/druginfo/18_2_2004.pdf>

———. 2004b. *The World Medicines Situation*. Geneva: WHO.

———. 2003. Regulation of Fixed-Dose Combination Products. *WHO Drug Information* 17(3):174–7.

★ ———. 1998. *Basic Tests for Drugs: Pharmaceutical Substances, Medicinal Plant Materials and Dosage Forms*. Geneva: WHO. <http://whqlibdoc.who.int/publications/1998/9241545135.pdf>

★ ———. 1997a. *Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*. Geneva: WHO. <http://whqlibdoc.who.int/hq/1997/WHO_PHARM_82.4_Rev.5.pdf>

———. 1997b. *Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials.* Vol. 1. Geneva: WHO.

———. 1995. *Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*. Geneva: WHO.

★ ———. 1994. *WHO Guidelines on Stability Testing of Pharmaceutical Products Containing Well-Established Drug Substances in Conventional Dosage Forms*. Geneva: WHO. <http://whqlibdoc.who.int/hq/1994/WHO_PHARM_94.565_rev.1.pdf>

———. 1990. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 31st Report. Geneva: WHO.

———. 1986. *Accelerated Stability Studies of Widely Used Pharmaceutical Substances under Simulated Tropical Conditions*. Geneva: WHO. <http://whqlibdoc.who.int/hq/1985-86/WHO_PHARM_86.529.pdf>

WHO/EURO (World Health Organization Regional Office for Europe). 1988. *The Investigation of Bioavailability and Bioequivalence.* (Draft.) Copenhagen: WHO/EURO.

WHO/UNICEF/UNDP/UNFP/World Bank (World Health Organization, United Nations Children's Fund, United Nations Development Programme, United Nations Population Fund, World Bank). 2007. *A Model Quality Assurance System for Procurement Agencies: Recommendations for Quality Assurance Systems Focusing on Prequalification of Products and Manufacturers, Purchasing, Storage and Distribution of Pharmaceutical Products*. Geneva: WHO. <http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf>