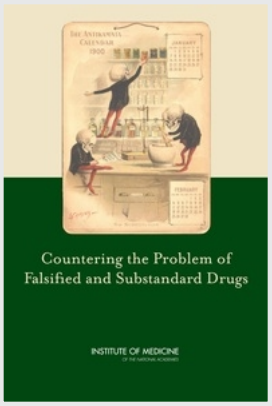

Countering the Problem of Falsified and Substandard Drugs

DETAILS

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Countering the Problem of Falsified and Substandard Drugs

Committee on Understanding the Global Public Health Implications of Substandard, Falsified, and Counterfeit Medical Products

Board on Global Health

Gillian J. Buckley and Lawrence O. Gostin, *Editors*

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Cover image from 1900 calendar produced by the Antikamnia ("Opposed to Pain") Chemical Company of St. Louis, Missouri (http://unitproj.library.ucla.edu/biomed/his/antikamnia/antikamnia.html).

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Harold Fallon,** Medical University of South Carolina, and **Elaine Larson,** School of Nursing and Mailman School of Public Health, Columbia University. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Acronyms and Abbreviations

ACTA	Anti-Counterfeiting Trade Agreement
ADDO	Accredited Drug Dispensing Outlet
AIDS	acquired immune deficiency syndrome
AMRH	African Medicines Regulatory Harmonization
Anvisa	National Health Surveillance Agency of Brazil
API	active pharmaceutical ingredient
BMI	*Business Monitor International*
CDC	Centers for Disease Control and Prevention
CHAI	Clinton Health Access Initiative
DFID	Department for International Development
DOTS	Directly Observed Treatment–Short Course
EMA	European Medicines Agency
ESI	electrospray ionization
EU	European Union
FDA	U.S. Food and Drug Administration
FIP	International Pharmaceutical Federation
GC-MS	gas chromatography and mass spectrometer
Global Fund	Global Fund to Fight AIDS, Tuberculosis, and Malaria

HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFC	International Finance Corporation
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
Medicrime Convention	Council of Europe Convention on the counterfeiting of medical products and similar crimes involving threats to public health
MSF	Médecins Sans Frontières (Doctors Without Borders)
MSH	Management Sciences for Health
NABP	National Association of Boards of Pharmacy
NGO	nongovernmental organization
NIST	National Institute of Standards and Technology
NSF	National Science Foundation
OECD	Organisation for Economic Co-operation and Development
OPIC	Overseas Private Investment Corporation
PhRMA	Pharmaceutical Research and Manufacturers of America
PQM	Promoting the Quality of Medicines
PSI	Pharmaceutical Security Institute
PSM	Partnership for Safe Medicines
RFID	radio frequency identification
SBIR	Small Business Innovation Research
SSFFC	substandard, spurious, falsely-labeled, falsified, counterfeit
TLC	thin layer chromatography
TRIPS	Trade-Related Aspects of Intellectual Property Rights
Unicef	United Nations Children's Fund
UNODC	United Nations Office on Drugs and Crime
USAID	United States Agency for International Development
USP	U.S. Pharmacopeia

VIPPS	Verified Internet Pharmacy Practice Sites
WCO	World Customs Organization
WHA	World Health Assembly
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization
WWARN	WorldWide Antimalarial Resistance Network

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BOXES

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Summary

The adulteration and fraudulent manufacture of medicines[1] is an old problem, vastly aggravated by modern manufacturing and trade. In the last decade, impotent antimicrobial drugs have compromised the treatment of many deadly diseases in poor countries. More recently, negligent production at a Massachusetts compounding pharmacy sickened hundreds of Americans. While the national drugs regulatory authority (hereafter, the regulatory authority) is responsible for the safety of a country's drug supply, no single country can entirely guarantee this today. Illegitimate[2] drugs are an international problem, and there is wide consensus that action depends on international cooperation.

Productive international discourse has been stymied, however, by disagreement about how to frame the problem. The once common use of the term *counterfeit* to describe any drug that is not what it claims to be is at the heart of the argument. In a narrow, legal sense, a counterfeit drug is one that infringes on a registered trademark. The lay meaning is much broader, including any drug made with intentional deceit. Some generic drug companies and civil society groups object to calling bad medicines counterfeit, seeing it as the deliberate conflation of public health and intellectual property concerns. This report accepts the narrow meaning of counterfeit, and, because the nuances of trademark infringement must be

[1] The terms *medicine*, *drug*, and *pharmaceutical* are used interchangeably in this report in accordance with the definitions listed in the *American Heritage Stedman's Medical Dictionary*.

[2] *Illegitimate*, as explained later in the report, is a parent category for falsified and substandard medicines.

dealt with by courts, case by case, the report does not discuss the problem of counterfeit medicines.

The trade in illegitimate drugs is, however, a problem of public health consequence and the topic of this report. In order to discuss this problem more precisely, the report distinguishes two main categories of poor-quality drugs. First, there are substandard drugs, those that do not meet the specifications given in the accepted pharmacopeia or in the manufacturer's dossier. The other main category of illegitimate products is falsified drugs, those that carry a false representation of identity or source or both. Many countries also have problems with unregistered medicines, those not granted market authorization in a country. Unregistered drugs may be of good quality, though some research indicates they often are not. Unregistered medicines usually circulate outside the controlled distribution chain and are therefore suspect.

The drug failures of public health concern can be divided into two main categories: falsified and substandard. Admittedly, the distinction between the two categories is not always clear. Falsified drugs are usually also substandard; national specifications referenced in the definition of a substandard drug can vary.[3] However, these terms cover the two main divisions of interest with sufficient precision. International endorsement of these two categories could advance public discourse on the topic.

Recommendation 1-1: The World Health Assembly should adopt definitions consistent with the following principles. Substandard drugs do not meet national specifications.[4] Falsified products have a false representation of identity or source or both. Products unregistered with the regulatory authority are also illegal.

The spirit of these definitions and the exclusion of the term counterfeit are central to this recommendation. The exact wording suggested is not.

THE HEALTH EFFECTS OF FALSIFIED AND SUBSTANDARD DRUGS

Falsified and substandard drugs may contain toxic ingredients; some of the most compelling stories of pharmaceutical crime are of frank poisoning. By far the more common problem, however, is medicine that simply does

[3] Some regulatory authorities may accept standards below those in international pharmacopeias. In such cases, a drug that would be generally regarded as substandard might be technically acceptable in a given country.

[4] An emphasis on quality system failures is not essential to the idea of a substandard drug and was removed from the recommendation after the report release. The supporting text describes the committee's understanding of a substandard drug.

not work. Poor-quality medicines cause treatment failure, but doctors do not generally suspect medicines as a cause of disease progression. Lifesaving medicines can be of poor quality, which may be an uncounted root cause of high mortality in low- and middle-income countries.

No class of drug is immune to being compromised. Medications for chronic and infectious diseases alike have been found falsified and substandard. A considerable body of research indicates that inexpensive antimicrobial drugs in low- and middle-income countries are frequently of poor quality. Such drugs not only put patients at risk but also encourage drug resistance, thereby threatening population health for future generations.

Substandard antimicrobials often contain low and erratic drug doses, while falsified ones can be diluted. In either case, exposing pathogens to subtherapeutic doses of medicines selectively allows the growth of resistant organisms. Poor-quality drugs have contributed to the rise of drug-resistant tuberculosis. Drug-resistant staphylococcus infections are an emerging problem, especially in India, Latin America, and sub-Saharan Africa. Antimalarial resistance threatens to undo the good that artemisinin therapies have done, threatening global malarial control programs.

THE ECONOMIC AND SOCIAL EFFECTS OF SUBSTANDARD AND FALSIFIED MEDICINES

Falsified and substandard drugs increase costs to patients and health systems. Medicines are expensive; patients and governments waste money on ineffective ones. Lingering illnesses decrease productivity, causing workers to forgo pay and spend more on treatment. Through encouraging antimicrobial resistance, illegitimate medicines reduce the effective life of a drug. Society must bear the cost of drug development, an expense that increases as drugs become more complex.

Substandard and falsified medicines undermine confidence in the health system and in all public institutions. Fake[5] drugs are often the business of criminal cartels. Their sale finances other crimes, buys weapons and ammunition, and conveys power to corrupt officials. Victims of falsified and substandard drugs usually do not even know they are victims and are therefore deprived of their right to redress. In many ways, the trade in illegitimate pharmaceuticals further erodes the already weak political infrastructure that allows them to circulate, part of a vicious cycle of poverty and crime.

[5] As the report explains later, *fake* is a commonly used synonym for *falsified*.

THE MAGNITUDE OF THE PROBLEM

It is difficult to measure the population burden of falsified and substandard drugs. Governments and industry monitor problems with drug quality, but this information is not usually public. The Pharmaceutical Security Institute, a network of the security divisions of 25 major pharmaceutical companies, has data that indicate that the illegal trade and manufacture of medicines is a global problem. It affected at least 124 countries in 2011, and the burden is disproportionately felt in the developing world.

Data from the U.S. Food and Drug Administration (FDA) Office of Criminal Investigations indicate that pills and tablets are the most commonly compromised products they investigate, mostly produced by individual criminals, not negligent businesses. Interpol, an international organization that facilitates police cooperation, has conducted 11 operations against illicit medicines since 2008. Police working in Interpol raids have confiscated tons of suspect products, leading to hundreds of investigations and arrests.

Much of the scientific literature about drug quality is in case studies: reports from clinicians who uncover substandard or falsified drugs in their routine work. This kind of report provides context on how and when different kinds of drugs are compromised; it can also trigger epidemiological investigation. Nonprobability or convenience samples are by far the most commonly used method to study drug quality. Such studies indicate serious problems with antibiotics in poor countries and antimalarial drugs in sub-Saharan Africa and Southeast Asia.

The best estimate of the burden of illegitimate drugs comes from systematic random samples, collected by patient actors from a representative cross section of drug sellers. Such studies are logistically complicated and few. More research in accordance with the recent guidelines on medicine quality assessment reporting would advance understanding and monitoring of the problem.

Lack of clarity regarding the magnitude of the falsified and substandard medicines market holds back coordinated international action. The World Health Organization (WHO) is developing a system for the global surveillance and monitoring of falsified and substandard drugs. Consistent use of this system, eventually linking it to national pharmacovigilance systems, would advance international action and give a more nuanced understanding of the type of falsified, substandard, and unregistered medicines in circulation and the extent of the trade.

Recommendation 3-1: Governments should establish or strengthen systems to detect substandard, falsified, and unregistered medicines. This surveillance should be integrated with established public health

surveillance systems. Analysis and reporting should precisely describe the product's quality, packing, and registration.

CAUSES OF SUBSTANDARD DRUGS

The factors that encourage the proliferation of falsified and substandard drugs are different but overlapping. Failure to adhere to good manufacturing practices is the root cause of substandard drugs. Quality-control processes and verification add expense to manufacture, as does maintaining sterile water filtration and air handling systems. Proper quality control includes dealing only with quality-assured suppliers, but small- and medium-sized manufacturers often neglect supplier quality because of logistical obstacles and cost.

Multinational companies, both innovator and generic, operate on a scale that allows them to recoup the costs of running high-quality factories. Initial capital investments and infrastructure problems stand between quality medicines and many small- and medium-sized medicine manufacturers. Small- and medium-sized firms and companies in Africa have a difficult time securing business improvement loans. The only capital available to these companies is their profits, and reinvesting profits is not a quick or reliable path to building a modern manufacturing infrastructure. The companies need hard currency loans, which their national banks cannot supply.

The International Finance Corporation and the Overseas Private Investment Corporation can work to encourage better private sector pharmaceutical manufacturing in developing countries. With the initial investments made, governments can take on the more manageable role of encouraging partnerships with foreign manufacturers.

Recommendation 4-1: The International Finance Corporation and the Overseas Private Investment Corporation should create separate investment vehicles for pharmaceutical manufacturers who want to upgrade to international standards. Governments can complement this effort by encouraging partnerships between local and foreign manufacturers.

In practice, it is difficult to distinguish the quality failures that are to blame on a manufacturer's inability to meet international best practices from those that come from a decision to cut corners and produce inferior products for poorly regulated markets. When a producer capable of meeting international standards fails to do so consistently and only in product lines sold to the poor, one may conclude that noncompliance is part of a more insidious system.

Rich countries enforce high quality standards for medicines, and manufacturers recognize the need to use quality ingredients and good manufac-

turing practices to sell in these markets. United Nations agencies and larger international aid organizations will also refuse to do business with companies that cannot meet stringent regulatory authority quality standards. Manufacturers are aware, however, that low- and middle-income countries are less likely to enforce these standards. When a manufacturer produces medicines of inferior quality for less exacting markets it is known as tiered or parallel production.

When regulatory checks on production are inconsistent, good procurement practices can ensure that quality medicines get the largest market share. The firms that offer the cheapest prices do so by buying impure ingredients and cutting corners in formulation. Good procurement dictates that the cheapest tenders are not accepted if they are of dubious quality, but it is difficult not to be swayed by price. Proper precaution in medicines procurement can prevent poor-quality products from infiltrating the market. Good procurement puts a strong emphasis on controlling corruption and promoting transparency. The WHO's Model Quality Assurance System for procurement agencies lays out the steps necessary for efficient and open procurement of the best-quality medicines possible.

Recommendation 4-2: Procurement agencies should develop a plan, within the next 3 to 5 years, to comply with the World Health Organization's Model Quality Assurance System for procurement agencies and work to remove any barriers to compliance.

CAUSES OF FALSIFIED DRUGS

In practice, one difference between falsified and substandard medicines is that the drugs regulator, having the authority to license manufacturers and register medicines, can act against unscrupulous or careless manufacturers. There is no such remedy when the manufacturer is falsely represented. The regulator can only confirm that the producer is unknown and turn the case over to law enforcement. The police and detectives who inherit these cases have a difficult job gathering sufficient evidence for a prosecution there is usually little if anything to tie the falsified drug in the market to the culprit.

Criminals run lucrative businesses making and trafficking fake medicines, and these crimes are mostly opportunistic, emerging where regulatory systems are weakest. When criminals target the products of multinational, innovator pharmaceutical companies, the companies' security staff build evidence for a conviction. Police are also investigating more pharmaceutical crimes, but most police action is limited to brief raids. It is difficult for police to keep up momentum for sustained action on pharmaceutical crime, especially given the immediate pressure to investigate murders and other violent crimes.

CAUSES OF BOTH FALSIFIED AND SUBSTANDARD DRUGS

Much as poor-quality drugs are often both falsified and substandard, some potentiating factors encourage both kinds of problems. The high demand and erratic supply of drugs, weak regulatory systems, and uneven awareness contribute to the trade in both falsified and substandard drugs.

Medicines are what economists describe as an inelastic good; changes in the unit price of the medicine have proportionately little effect on the demand. Price inelasticity, combined with a high relative price, make medicines a major expense for patients around the world. The drug market is not stable; both price and supply fluctuate. Drug shortages drive up the price of medicines and push consumers to unregulated markets.

Reducing the costs and increasing the availability of medicines would help prevent drug scarcity. The WHO has recommended generic substitution as a way to keep medicine costs down, but this depends on a supply of quality generic medicines on the market. For generic manufacturers, companies that generally run on low margins, the costs of proving bioequivalence and preparing a manufacturer's dossier for regulatory review can be prohibitive to market entry. Different regulatory authorities have different, often widely divergent, requirements. To complicate the problem, many small regulatory authorities lack the technical depth to evaluate the bioequivalence data that generics manufacturers submit.

The high cost of market authorization impedes the development of a strong generics industry in poor countries. A more robust generic drug market could help prevent the drug shortages and price spikes that encourage the sale of poor-quality products. Regulatory authorities can work to better harmonize their procedures, thereby improving their own efficiency and reducing barriers to market entry for good-quality generics manufacturers. The use of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Common Technical Document format for registration would ease the regulatory burden on generics companies. Regulators also reap a spillover benefit of more convergent regulatory systems without negotiating cumbersome mutual recognition agreements.

Recommendation 4-3: Regulatory authorities in low- and middle-income countries should use the International Conference on Harmonisation Common Technical Document format for product registration to better harmonize their procedures and reduce application costs for manufacturers. To the same end, they should also conduct joint inspections and use a common inspection report.

An influx of generic medicines will only reduce the circulation in falsified and substandard drugs when there is a system to assure consumers of medicines' quality. A functioning medicines regulatory authority is a necessary condition for a robust generic medicines market. Strengthening the drugs regulatory system, building the inspectorate, enforcing quality standards, and licensing in accordance with international standards are essential to improving drug quality. Without a competent regulatory authority to inspect wholesalers, distributors, and manufacturers, opportunities to corrupt the drug supply abound.

A strategy for compliance with international standards can help reduce redundant work and fragmentation. Both industry and regulators should agree to work toward the priorities identified in the strategic plan, an openly shared document.

Recommendation 4-4: Governments in low- and middle-income countries should support their regulatory agencies to develop strategic plans for compliance with international manufacturing and quality-control standards. In the least developed countries, international organizations should support their efforts.

Large pharmaceutical manufacturing nations such as India and China suffer from fragmented regulatory systems and an unclear division of responsibilities between state and national governments. The United States has similar problems, evidenced by the recent fungal meningitis outbreak brought on by a contaminated injectable steroid drug, compounded under unhygienic conditions at the New England Compounding Center. Lack of clarity about the relative authority of the FDA and state pharmacy councils to regulate compounding pharmacies contributed to the outbreak. Neither the state of Massachusetts nor the FDA had clear control over the New England Compounding Center. Confusion about their responsibilities created a regulatory gap. Similar confusion causes regulatory gaps in other countries where national and local governments share responsibilities for drug regulation.

During times of crisis, such as the meningitis outbreak, public interest in drug quality peaks, but it can be difficult to maintain. Patients in developed countries have long taken a safe drug supply for granted. They may not realize the risks of circumventing the regulated distribution system. In poor countries, patients are often more aware of the problem, but there are knowledge gaps, especially among the poorest and least educated. Effective communication campaigns can raise awareness of the problem and give consumers empowering messages on how to protect themselves. Such campaigns have effectively promoted change in rich and poor countries alike.

Recommendation 4-5: Governments and donor agencies should fund development of effective communication and training programs for consumers and health workers on understanding the quality and safety of medicines.

Targeted health worker education on falsified and substandard medicines would improve understanding of the problem around the world. This education should emphasize the correct reporting channels health workers can use to confirm suspected cases of bad drugs. Illegitimate drugs are a potential threat in all countries, though risk varies widely from country to country. An effective communication campaign should present accurate information in a way that empowers patients to protect their health.

THE DRUG DISTRIBUTION CHAIN

The modern pharmaceutical supply chain is complex. Medicines are made from ingredients sourced from different countries. Final formulations are then exported, and packaging, repackaging, and sale can happen in many other countries. Drugs change hands many times between the manufacturer and patient; every transaction is an opportunity for falsified and substandard products to infiltrate the market. Drug quality around the world could be improved with changes to the drug distribution system.

The systems differ markedly between developed and developing countries, however. Fewer, larger firms control manufacture and the wholesale drug markets in developed countries, where most patients get medicines from licensed pharmacies or dispensaries. In low- and middle-income countries, multiple parallel distribution systems of varying efficiency run in the same country. It is also difficult and expensive to transport medicines over poor roads to remote villages, as supply chain managers in poor countries must do.

The first step on the drug distribution chain is the wholesale market. There are two kinds of drug wholesalers: primary wholesalers who have written distribution contracts with manufacturers and buy directly from them, and secondary wholesalers who buy from other intermediaries. Both kinds of wholesalers buy and sell medicines to accommodate market demand. When they see that a medicine is scarce in one region, they can buy the same medicine from other wholesalers that may be flush with it. The markets are constantly fluctuating; products change hands many times. Wholesalers may repackage products repeatedly, and in the repackaging fake products can gain authentic labels.

In the United States, thousands of secondary wholesalers trade medicines, causing drug shortages and exploiting them for profit. Limiting the

secondary wholesale market to vetted firms would improve the U.S. drug supply. The National Association of Boards of Pharmacy (NABP) wholesaler accreditation process requires criminal background checks on senior staff and proof of professional standards in record keeping and drug storage and handling. Some states require NABP accreditation of wholesalers, but unscrupulous businesses can seek out states with lower standards for their headquarters. And, because the wholesale trade is national, weaknesses in one state's system can become vulnerabilities in another.

Recommendation 5-1: State licensing boards should only license wholesalers and distributors that meet the National Association of Boards of Pharmacy accreditation standards. The U.S. Food and Drug Administration, in collaboration with state licensing boards, should establish a public database to share information on suspended and revoked wholesale licenses.

Similar weaknesses plague the wholesale system in developing countries, and action in the American market might give regulators around the world example and encouragement to tighten controls on the chaotic wholesale market.

More stringent licensing requirements can improve the wholesale system, but drugs will still need to move from factory to the vendor, passing through many hands before reaching the patient. With every transaction on the chain, there is a risk of the drug supply being compromised. Criminals take advantage of places where the distribution chain breaks down and medicines depart from the documented chain of custody. Drugs that leave the proper distribution system are called diverted drugs; the markets that trade diverted drugs or, more generally, markets that trade with little authorized oversight are called gray markets.

Drug diversion is the means through which medicines approved for sale in one country are sold in others, where they may not be registered. Small thefts and large heists compromise the integrity of the drug distribution chain and confidence in the quality of medicines. In rich and poor countries alike, drugs often circulate outside of the main distribution channels without a drug pedigree, a record of a drug's every sale and owner.

Drug pedigrees depend on attaching some form of unique identifying numbers to products. Products that lack identification numbers, or products with identification numbers that cannot be accounted for throughout the distribution chain, must be treated as falsified and removed from the market even if they come from licensed manufacturers. Radio frequency identification, traditional and two-dimensional barcodes, and mobile verification are methods for serialization that can facilitate drug tracking.

Recommendation 5-2: Congress should authorize and fund the U.S. Food and Drug Administration (FDA) to establish a mandatory track-and-trace system. In the interim, the FDA should convene a working group of stakeholders, including the International Federation of Pharmaceutical Manufacturers and Associations and the Generic Pharmaceutical Association, to promote voluntary track-and-trace for all supply chain actors in accordance with existing guidance.

Tracking pharmaceuticals through the global distribution chain with unique serial numbers is a good defense against criminal infiltration. A method of tracking individual packages of medicines from the factory to the consumer could greatly reduce the chances of a dangerous product being sold at a reputable pharmacy. Problems will remain, however, with unlicensed drug shops. Medicines retail, the last leg of the drug distribution system, is often the most chaotic.

The drug distribution system becomes more disordered as the products leak out of regulated distribution chains. The risk increases as drugs move farther from manufacturer. Licensed pharmacies and dispensaries can control the quality of their stock, at least insomuch as they can trust their wholesalers. There are no such efforts at quality control in the unlicensed market. Unlicensed vendors may approach medicines dispensing as any other sales job and not want a customer to leave without making a purchase. In general, these vendors exploit the chaos inherent to street markets and dry goods shops in low- and middle-income countries and online drug stores in middle- and high-income ones.

A simple lack of alternatives pushes consumers in developing countries to buy medicine from unlicensed vendors, who may sell pills loose from large plastic bags or subdivide blister packs. Despite this and other gross violations of good practice, the shops often operate with the regulators' tacit approval, because they are the only source of medicines outside of major cities.

There are also too few trained pharmacy staff in developing countries, especially in sub-Saharan Africa and South and Southeast Asia. In many countries, the few trained pharmacists work in industry. Community pharmacy practice, especially in rural areas, suffers. Having a trained community pharmacist oversee every drug store is not an option in the parts of the world most hurt by falsified and substandard medicines. Governments should take action to increase the reach of legal drug shops staffed by sellers with appropriate minimum training.

Recommendation 5-3: Governments in low- and middle-income countries should provide an environment conducive to the private sector establishing high-quality medicines retail in underserved areas. Govern-

ment incentives could encourage this. To the same end, governments, the World Health Organization, and the International Pharmaceutical Federation should support national pharmacy councils and education departments to train tiers of pharmaceutical personnel.

The private sector will invest in medicines retail if there is a good business reason to do so. Governments can take steps that would encourage private sector investment and create an environment where responsible private drug sellers will thrive. Governments can provide low-interest loans for improving drug shops and encourage private-sector accreditation or franchising programs. They can also work with their national pharmacy councils to set out tiers of training, including vocational training, for pharmaceutical personnel. Governments can also give incentives to keep trained staff in underserved areas.

Disorganized medicines retail is not confined to developing countries. Through the internet, unlicensed drug vendors sell around the world, mostly in middle- and high-income countries. Unlicensed internet pharmacies are similar to street drug bazaars, both in the quality of the products they stock, which is poor, and in the lack of official oversight of their operations.

In the United States the NABP runs the Verified Internet Pharmacy Practice Sites (VIPPS) accreditation program to recognize safe online drug stores. Accredited online pharmacies comply with state licensing requirements for both the state that the pharmacy is in and all the states in which it sells. Chief among these requirements are the authentication of prescriptions, observance of quality-assurance standards, and submission to regular state inspection. Accredited pharmacies display the VIPPS seal, and, because this seal could be copied, the project website lists both certified pharmacies and known fraudulent ones.

DETECTION TECHNOLOGY

The main categories of techniques for pharmaceutical analysis can be broken down as visual inspection of product and packaging; tests for physical properties such as reflectance and refractive index; chemical tests including colorimetry, disintegration, and dissolution; chromatography; spectroscopic techniques; and mass spectrometry. Within each of these categories, some technologies are appropriate for field use, while others require sophisticated lab equipment and a high level of technical expertise.

Understanding when, where, and why to use the various techniques can be difficult. The information a technique provides, as well as its reliability, cost, speed, and portability, make it more or less appropriate in any given situation. While any one test may suffice to label a drug substandard or falsified, no single analytical technique provides enough information

to confirm that a drug is genuine. One challenge in both field and laboratory testing is determining how to combine tests for maximum efficiency. It is usually best to work through tests beginning with the easiest or least expensive ones. Only if samples pass these tests should the inspector move on to more difficult or expensive ones.

Making detection technology more accessible in low- and middle-income countries would be invaluable to controlling the trade in falsified and substandard drugs. Technologies can protect consumers and are useful to surveillance staff working to generate accurate estimates of the magnitude of the problem of poor-quality drugs. An understanding of the technological landscape, the range and gaps in available technologies, and the likely improvements in the near future is essential for using technologies in developing countries.

Recommendation 6-1: The National Institute of Standards and Technology should fund the development of a central repository for existing and newly innovative detection, sampling, and analytical technologies, ranging from field and rapid screening technology to sophisticated laboratory-based assessments, to identify substandard and falsified medicines.

CODE OF PRACTICE

Individual countries have the responsibility for protecting the national drug supply. This includes regulating good-quality manufacturers, preventing poor-quality drugs from entering the market, detecting them when they do, and punishing those who manufacture and trade them. Drug regulation, surveillance, and law enforcement are the necessary components of any national response to the problem.

A voluntary soft law such as an international code of practice could encourage international action against falsified and substandard drugs. The code of practice would contain guidelines on surveillance and international reporting of drug quality problems. The code would facilitate passage of national laws on how to punish and, when necessary, extradite those responsible for falsified drugs and criminally negligent manufacture. It would also promote harmonized regulatory standards for drug manufacture and licensing.

Recommendation 7-1: The World Health Assembly, in partnership with the United Nations Office on Drugs and Crime and the World Customs Organization, and in consultation with major stakeholders, should institute an inclusive, transparent process for developing a code of practice on the global problem of falsified and substandard medicines.

The code should include guidelines on surveillance, regulation, and law enforcement, empowering states and the international community to prevent and respond to drug quality problems.

The manufacture and trade in falsified medicines is a growing, global problem. It is difficult to estimate the amount of falsified and substandard drugs in the market or to know the toll these products take on society, the number of deaths or excess illness they cause, or the amount of time and money wasted using them in treatment. There is evidence from some convenience surveys that antimicrobial drugs are often compromised in Southeast Asia and sub-Saharan Africa. In a larger sense, all drugs sold outside of legitimate chains are suspect. This includes medicines sold in unregulated markets and most drugs sold on the internet.

This report suggests a combination of actions that could reduce the global trade in falsified and substandard medicines. Some recommendations aim to improve medicine quality in the low- and middle-income countries that unquestionably bear a disproportionate burden of the problem. Other recommendations could improve weaknesses in the U.S. system, which would help the American consumer and build momentum for global action. Eliminating falsified and substandard drugs from the market requires international cooperation. A voluntary soft law could help advance harmonized systems for surveillance, regulation, and law enforcement.

1

Introduction

In the 1949 film *The Third Man* and the novel of the same name, Holly Martin learns that his childhood friend Harry Lime has made a fortune diluting stolen penicillin and selling it on the black market. In a dramatic confrontation on the Vienna Ferris wheel, Martin refers to Lime's earlier racketeering, asking, "Couldn't you have stuck to tires?" No, explains Lime, one of the American Film Institute's 100 greatest villains, "I've always been ambitious" (AFI, 2003).

The theft, adulteration, careless manufacture, and fraudulent labeling of medicines[1] continue to attract villains who, like Harry Lime, grow wealthy off their business. Although the problem is most widespread in poor countries with weak regulatory oversight, it is no longer confined to underground economies as in postwar Vienna. As of January 2013, gross manufacturing negligence at a compounding pharmacy in Massachusetts had sickened 693 Americans and killed 45 (CDC, 2013). Less than a year earlier, 76 doctors in the United States unknowingly treated cancer patients with a fake version of the drug Avastin (Weaver and Whalen, 2012).

International trade and manufacturing systems obscure connections between the crime and the criminal; in modern supply chains, medicines may change hands many times in many countries before reaching a patient. To complicate the problem, medicines are mostly for sick people. The effects of inactive, even toxic, drugs can go unnoticed or be mistaken for the

[1] The terms *medicine*, *drug*, and *pharmaceutical* are used interchangeably in this report in accordance with the definitions listed in the *American Heritage Stedman's Medical Dictionary* (2012a,b,c).

natural course of the underlying disease. This is most true in parts of the world with weak pharmacovigilance systems, poor clinical record keeping, and high all-cause mortality, where "friends or relatives of those who die are obviously saddened, but not necessarily shocked" (Bate, 2010).

Deaths from fake drugs go largely uncounted, to say nothing of the excess morbidity and the time and money wasted by using them. The manufacture and trade in fake pharmaceuticals is illegal and hence almost impossible to measure precisely. Even crude copies can blend in with legitimate products in the market. The camouflage succeeds because drug quality is not something consumers can accurately judge. This imbalance, also called information asymmetry, makes the medicines trade vulnerable to market failure (Mackintosh et al., 2011). In short, "At every step of the supply chain there is this unequal knowledge, and people are exploited because of [it]" (Mackintosh et al., 2011, p. 2).

Market controls and oversight aim to correct the information imbalance in the medicines market, but supervising sprawling multinational distribution chains is a "regulatory nightmare" (*Economist*, 2012). National drugs regulatory agencies (hereafter, regulatory agencies) are responsible for assuring drug quality in their countries, a job that increasingly requires cooperation with their counterpart agencies around the world (IOM, 2012). The World Health Organization (WHO) has worked to facilitate this cooperation since 1985, but advancing the public discourse on this topic has proven more difficult than anyone would have predicted then (Clift, 2010).

To start, different countries and international stakeholders cannot agree on how to define the problem. When it is framed as one of counterfeit and legitimate drugs, many civil society groups and emerging manufacturing nations see a thinly veiled excuse to persecute generic drug industries (Clift, 2010; *Economist*, 2012). Large innovator pharmaceutical companies have the most experience in finding and prosecuting pharmaceutical crime. This expertise brought them a place in the WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT), the largest international working group on drug safety to date. Involving these companies with a WHO program, however, raised suspicions of civil society groups (TWN, 2010). Objections to the taskforce's inception and confusion about its mandate from WHO governing bodies further eroded support (TWN, 2010). The WHO distanced itself from IMPACT after 2010; the taskforce's secretariat moved to the Italian drugs regulatory authority (Seear, 2012; Taylor, 2012).

IMPACT may no longer be active, but criminals and unscrupulous drug manufacturers are. The *Economist* recently described the 21st century as "a golden age for bad drugs" (*Economist*, 2012). There is an urgent need for international public discourse on the problem. In an effort to advance this discourse, the U.S. Food and Drug Administration (FDA) commissioned

the Institute of Medicine (IOM) to convene a consensus committee on understanding the global public health implications of falsified, substandard, and counterfeit pharmaceuticals. Box 1-1 presents the committee's charge. (See Appendix B for committee member biographies.)

The committee met in March, May, July, and October of 2012 to hear speakers and deliberate on its recommendations for this report. Small travel delegations of committee members and staff also visited experts in Brasília, Delhi, Geneva, Hyderabad, London, and São Paulo in the summer of 2012. In total, the committee heard input from 106 experts in its information gathering meetings. (See Appendix C for meeting agendas.) Additional literature review informed the conclusions and recommendations presented in this report.

BACKGROUND AND TERMS

The committee's first step in deliberating on the task in Box 1-1 was agreeing on common terms to describe the products of interest. They reviewed the competing and often overlapping definitions of the terms *counterfeit*, *falsified*, and *substandard*, as well as similarly important concepts such as *unregistered*. As Tables 1-1 through 1-6 make clear, some of these definitions have evolved over time, with the trade and intellectual property debates of the last 20 years coloring how people use words like counterfeit. The following brief background on intellectual property, public health, and patent and trademark infringement gives some context to this discussion.

Key Findings and Conclusions

- A long and acrimonious history of applying intellectual property rights to medicines colors the discussion about drug quality.
- A counterfeit medicine is one that infringes on a registered trademark. The broad use of the term *counterfeit*, meaning made with intention to deceive, is insufficiently precise for formal, public discourse.
- Substandard drugs fail to meet the specifications outlined by an accepted pharmacopeia or the manufacturer's dossier.
- Falsified drugs are those that carry false representation of identity or source.
- Unregistered drugs circulate without market authorization. Unregistered medicines are suspect, though some may be of good quality.

BOX 1-1
Statement of Task

The Institute of Medicine (IOM) is requested to convene an ad hoc consensus committee of diverse experts to gather information and deliberate on approaches to mitigating the global problem of substandard, falsified, and counterfeit pharmaceuticals and products used in their manufacture. It will begin by developing among the committee members and for this context consensus working definitions for the terms *substandard*, *falsified*, and *counterfeit*. The committee will carefully distinguish between the application of these terms to meet public health and legal needs. Then, focusing specifically on the public health aspects of the problem, the IOM committee will address the following issues:

- Trends: Using available literature, identify high-level, global trends in substandard, falsified, and counterfeit (SFC) medicines, including differences and similarities in different global regions. Identify gaps in the evidence that complicate the analysis of these trends. This is intended to provide context to the study but not to serve as an in-depth analysis.
- Risks in the supply chain: Identify the weaknesses in the supply chain that allow falsified, substandard, and counterfeit drugs to circulate.
- Health effects: Explain the public health consequences, to patients and at the population level, of SFC drugs and how to measure this.
- Standards: Identify areas where convergence of standards could contribute to stronger regulatory actions.

Intellectual Property and Public Health

Intellectual property rights, particularly patent rights, allow the owner of a new product or technology to recoup their research and development costs by charging prices far above the marginal cost of production. Therefore, patent-protected medicines are expensive; the cost of these drugs puts them out of the reach of many patients. In developed countries, governments or large private insurers can mitigate this problem (Rai, 2001). But in poor countries, health insurance is limited and noncompetitive pricing can exclude entire countries from the medicines market (Yadav and Smith, 2012).

TRIPS and the Doha Declaration

The recent history of the international patent controversy began with the 1994 Agreement on Trade-Related Aspects of Intellectual Property

- Identification: Describe global regulatory processes (e.g., track-and-trace, authentication) that distinguish genuine and high-quality drugs from fake or substandard drugs and identify what factors could be used for additional scrutiny of the genuineness of the product.
- Technology: Identify detection, sampling methods, and analytical techniques used to identify counterfeit, falsified, and substandard drugs. Explain how these technologies can be best used and implemented in a system to stop the circulation of harmful drugs.
- Collaboration: Assess effectiveness of regulatory approaches around the globe, including prevention, detection, track-and-trace systems, compliance, and enforcement actions.
  - Based on such an assessment, identify areas where collective action among government regulatory authorities is most relevant and sustainable;
  - Identify ways government, industry, and other stakeholders can work together to strengthen supply chains and fight counterfeit, falsified, and substandard drugs;
  - Identify areas where industry or other stakeholders are best equipped to act; and
  - Recommend a collaborative path forward. This includes recommending definitions for the products in question that would be sensitive to the needs of drug regulators around the world and focuses on the public health. It also includes recommending how various regulators could collaborate on a global and regional level to best address the problem.

Rights (TRIPS), which required signatories to make patents available, either immediately or after a transition period (Barton, 2004; WTO, 1994). However, a provision allowed governments to grant compulsory licenses, that is, to grant a license to use a patent without the patent holder's consent, subject to conditions laid down in the agreement (WTO, 1994). Compulsory licenses are subject to prior negotiation with the patent holder, but these negotiations too can be waived in cases of national emergency or extreme urgency or for public noncommercial use (WTO, 1994).

As TRIPS entered into force, antiretroviral drugs for HIV and AIDS were becoming widely available in developed countries, reducing AIDS mortality dramatically within 4 years (CASCADE Collaboration, 2003; Osmond, 2003). The expense of the patent-protected drugs put them out of reach for all but 2 percent of the approximately 2.5 million HIV and AIDS patients in low- and middle-income countries (WHO, 2002). Tensions over patent protection came to a head in 2001 when the Pharmaceutical

Research and Manufacturing Association, representing 39 major pharmaceutical companies, sued the South African government over a law that allowed the manufacture of patent-protected AIDS drugs (BBC, 2001a; Simmons, 2001). The association "bow[ed] to mounting public pressure" and dropped the case after disastrous press (BBC, 2001b; *Economist*, 2001; Pollack, 2001; Swarns, 2001). After 2001, innovator drug companies began issuing more voluntary licenses at lower prices (Flynn, 2008).

Antiretrovirals would still have been too expensive for the poorest patients if not for Indian drug companies, exempted from TRIPS patent protections until 2005. In February 2001, the Indian drug company Cipla offered its triple therapy combination of stavudine, nevirapine, and lamivudine to Doctors Without Borders (an organization known by the French acronym MSF [Médecins Sans Frontières]) for less than $1 per patient per day, undercutting the cheapest voluntary license offer by about 65 percent (McNeil, 2001; t'Hoen et al., 2011).

More recently, regulators and innovator pharmaceutical companies have devised other ways to make patent-protected drugs available in developing countries. The U.S. government uses the FDA tentative approval process to guarantee drugs supplied through the President's Emergency Program for AIDS Relief (FDA, 2013). Through this program, the FDA approves both drug combinations (many not available in the United States because of patent controls) and the producers in Asia and Africa that make the drugs at greatly reduced costs (FDA, 2013). Drugs granted tentative approval "[meet] all safety, efficacy, and manufacturing quality standards for marketing in the U.S., and, but for the legal market protection, . . . would be on the U.S. market" (FDA, 2013).

Patent and Trademark Infringement

Patents, not trademark or trade dress, are the main source of tension between intellectual property and public health. But both patent and trademark questions surfaced in 2008 and 2009 when European customs officials seized consignments of generic medicines in transit from India to Latin American and sub-Saharan Africa (Brant and Malpani, 2011). The drugs were not under patent in India, nor in the counties they were destined for, but a European Union (EU) regulation allows customs officials, acting either on their own behalf or after a request from the rights holder, to seize goods that may infringe on patents, trademarks, or copyrights (Ho, 2011; Miller and Anand, 2009). Dutch courts interpreted this to mean that customs authorities are allowed to treat in-transit goods as if they had been made in Holland (Ho, 2011). French and German customs officials also seized drug shipments in the same period (Taylor, 2009).

Sometimes trademark misunderstandings delay consignments. In May

2009, German authorities suspended a shipment of amoxicillin bound for Vanuatu in the Frankfurt airport on the grounds that it might infringe on GlaxoSmithKline's trademark name for the same drug, Amoxil. When contacted, GlaxoSmithKline denied any suspicion of trademark infringement, by which time the shipment had been delayed for 4 weeks (Mara, 2009; Singh, 2009).

Whether the use of national law to seize in-transit drug shipments is consistent with international law, particularly the TRIPs agreement, remains an open question (Ho, 2011; Ruse-Khan, 2011). Developing countries argue that such seizures violate TRIPs agreement safeguards allowing the export of cheap generic drugs to countries unable to manufacture them (Ho, 2011). On the other hand, the Anti-Counterfeiting Trade Agreement, signed by Australia, Canada, the European Union, Japan, Korea, Morocco, New Zealand, Singapore, and the United States, does allow parties to enforce their national trademark law against goods-in-transit, thereby potentially endangering certain generic shipments[2] (USTR, 2011).

In any case, there are ambiguities in determining trademark infringement. U.S. law, for example, determines trademark infringement based on likely consumer confusion, something the 13 federal circuits employ 13 different multifactor tests to identify (Beebe, 2006). Drug trademarks can be contentious when companies register trademark names similar to the nonproprietary name (as in the case of Amoxil and amoxicillin) and when drug manufacturers attempt to trademark characteristics such as color.

TRIPS requires World Trade Organization (WTO) member countries to treat "willful trademark counterfeiting . . . on a commercial scale" as a criminal offense[3] (Clift, 2010). This kind of crime may be different from the civil offense of trademark infringement, if the willfulness of the crime is unclear, for example, or if the trademark is not identically copied (Clift, 2010). These distinctions are not important to some stakeholders. As a 2011 Oxfam policy paper explained, "whether a falsely labeled, substandard, or unregistered product is also the result of willful trademark infringement on a commercial scale, as criminalized under the TRIPS Agreement, is irrelevant from the perspective of public health" (Brant and Malpani, 2011, p. 23).

Oxfam's point is well taken. The goals of patent and trademark law are not those of public health. Trademarks can give an incentive to invest in quality and cultivate a brand loyalty, but this depends on consumers' evalu-

[2] Anti-Counterfeiting Trade Agreement (ACTA). October 1, 2011.

[3] TRIPS: Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, THE LEGAL TEXTS: THE RESULTS OF THE URUGUAY ROUND OF MULTILATERAL TRADE NEGOTIATIONS 320 (1999), 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994).

ating quality correctly, something difficult to do with medicines (Landes and Posner, 1987). The inability of the consumer to evaluate drug quality is the reason why medicines quality is monitored by an independent, government regulatory agency. The courts enforce trademark and patent laws; drugs regulators enforce quality standards. It is unreasonable and unfair to mix those jobs. Such was the logic of the International Negotiating Body on a Protocol on Illicit Trade in Tobacco Products, which recently removed all references to counterfeits from its treaty, noting that decisions about trademark infringement in tobacco products was not within their purview (New, 2012).

The committee recognizes that many poor-quality medicines also infringe on registered trademarks. At times, trademark infringement can *become* a public health problem, but it is not a public health problem in itself, even insomuch as it pertains to medicines.

Competing Meanings of the Term Counterfeit

The contentious history of drug patent and trademark enforcement colors discussions of drug quality, particularly the use of the term counterfeit. The U.S. Code, the WTO, the TRIPS Agreement, and Oxfam all use the legal meaning of a counterfeit medicine as one that infringes on a registered trademark (Brant and Malpani, 2011; Clift, 2010; WTO, 1994, 2012). Nevertheless, the word counterfeit, like material and harmless, means one thing to lawyers and judges and something else in common discourse. It is the widely used common meaning of counterfeit as "made in exact imitation of something valuable with the intention to deceive or defraud" (*Oxford Dictionaries*, 2012) that inspires the way the term is used by the WHO, the Pharmaceutical Security Institute, the Council of Europe, and the governments of India, Kenya, Nigeria, Pakistan, and, in some cases, the United States (see Table 1-1). The WHO definitions of counterfeit lean on the intent to deceive; Table 1-1 shows how most WHO definitions use the words "deliberately and fraudulently mislabeled."

There is elegance to a definition that stresses the intention to deceive. Its proponents rightly observe that this is what most people understand the word to mean anyway. This definition has at its center the effort to distinguish between deliberate and accidental problems. The manufacturer is not to blame if a drug is sold after the expiry date or if it has been kept in conditions that encourage rapid degradation. The 2008 contamination of Baxter heparin was a reminder that even expert companies sometimes produce bad products, but the failure was not intentional (Attaran and Bate, 2010). The regulatory system typically punishes such mistakes, whereas the law enforcement system punishes intentional crimes.

In practice, however, it is extremely difficult to distinguish accidental

and intentional problems in drug manufacture. Making the distinction, like determining trademark infringement, is a matter for the courts. Furthermore, competing meanings of the word counterfeit—one narrow, meaning infringement on a registered trademark, and one broad, meaning intentionally deceptive—frustrate many.

When bad drugs are all called counterfeit, some see in this definition an attempt to conflate the enforcement of intellectual property rights and protection of public health (Brant and Malpani, 2011; Clift, 2010; MSF, 2012; Oxfam International, 2011; TWN, 2010). International nongovernmental organizations (NGOs), such as Oxfam and MSF, are concerned with access to medicines in the world's poorest countries, access that cannot be possible without the generics companies that produce medicines for a fraction of the cost innovator companies charge. Generics companies may be vulnerable to accusations of trademark infringement or even deception. When a generic and an innovator drug company market bioequivalent medicines under similar-sounding names or with similar-looking pills, it is debatable whether or not these characteristics are copied or made with an intention to deceive the consumer. These are questions for the courts to decide case by case.

Counterfeit is a word that almost everyone uses to talk about bad medicines, but as Tables 1-1 and 1-2 indicate, often with widely divergent meanings. The ambiguity confuses discussions even within governments. The FDA, for example, endorses on its website a definition different from that in the U.S. Code or that used by the Department of Justice and other U.S. government agencies. The use of the word counterfeit to describe any poor-quality drug does not serve the cause of intellectual precision or productive discussion. The committee accepts the narrow, legal meaning of a counterfeit drug as one that infringes on a registered trademark. Trademark infringement is not a problem of public health concern, nor, in most cases, is it even readily identifiable. Drug companies, both innovator and generic, have the legal right to challenge counterfeiting; sorting out the nuances of trademark infringement should be left to the courts.

This report is about drug quality as a public health problem; it is not concerned with trademark infringement. Therefore, this report does not discuss the problem or solutions to the problem of drug counterfeiting, or make mention to counterfeit drugs, *except in cases where to do otherwise would be a misrepresentation of someone else's work*. Scientific literature and public health campaigns, especially those more than 2 or 3 years old, often describe poor-quality drugs as counterfeit. The committee hopes that all parties will break this habit but believes that most speakers who use the term use it broadly with no ulterior motives or ill will toward generics.

Substandard and Falsified Drugs

Use of the term *substandard* is less controversial (see Tables 1-3 and 1-4). There is consensus among most organizations that substandard drugs are those that fail to meet established quality specifications. When regulators approve a drug, they approve a quality standard, outlined in the accepted pharmacopeia or in the manufacturer's approved dossier. As the WHO explains, substandard products "do not meet the quality specifications set for them in national standards" (WHO, 2009).

As Table 1-3 indicates, the emphasis on national standards is a relatively recent change to the definition of a substandard drug. Before 2009, the emphasis was on an official pharmacopeia, not the national standard. Critics of the addition point out that the regulatory authority is responsible for approving national drug standards, a job that exceeds its capacity in many low- and middle-income countries (Ravinetto et al., 2012). Accepting the national standard might appear to endorse multiple, possibly inadequate standards (Ravinetto et al., 2012).

On the other hand, an emphasis on national standards improves the precision of the definition. There are many internationally accepted pharmacopeias; some give, for example, different acceptable ranges for drug concentration.[4] The committee agrees with the WHO's 2009 revision to the definition of substandard to specify the standards authorized by the national regulatory authority. It is more practical to let the national regulatory authority name the standard for a drug and test against that standard. In any case, most countries use standards set out in the large, international pharmacopeias. More than 100 nations, including most of the Commonwealth, accept British Pharmacopoeia standards (GIZ, 2012); 140 recognize the U.S. Pharmacopeia (USP, 2013), and 37 the European Pharmacopoeia (Council of Europe, 2013). (Some countries reference different pharmacopeial standards for different drugs and may therefore officially use more than one pharmacopeia.)

Some understandings of a substandard medicine emphasize the manufacturer's market authorization. (See Table 1-3.) This distinction becomes important when a substandard product is found in commerce. The regulatory agency can then take corrective action with the manufacturer and recall other products from the same batch. During this process, the manufacturer may prove with verified records and batch samples that the poor-

[4] For amodiaquine hydrochloride tablets, the acceptable drug concentration range under U.S. Pharmacopeia is 93 percent to 107 percent of labeled amount (USP, 2011a); under International Pharmacopoeia it is 90 percent to 110 percent (WHO, 2011c). For quinine sulfate tablets, the acceptable drug concentration range under U.S. Pharmacopeia is 90 percent to 110 percent of the labeled amount (USP, 2011b); under British Pharmacopoeia, it is 95 percent to 105 percent (British Pharmacopoeia, 2012c).

quality drug is not in fact its own. In such a case, the manufacturer is the victim of fraud. The drug in question was falsified and therefore in the domain of law enforcement.

The committee considers a drug *falsified* when there is false representation of the product's identity or source or both. Falsified medicines may contain the wrong ingredients in the wrong doses. A fake product in legitimate packaging is falsified, as is a good-quality product in fake packaging (EMA, 2012). The producer's intention is theoretically important to the understanding of a falsified drug, though in practice it is often impossible to known what these intentions were. That is, when a licensed manufacturer makes bad drugs, the deliberateness of the mistake is at least debatable. When an underground producer makes a bad-quality product there is not even a pretense of adhering to drug quality standards. This understanding of a falsified medicine is consistent with the broad definition of counterfeit used by WHO and other organizations. A falsified drug may also be called fake, a synonym used in this report and by some scholars, governments, and international NGOs (Bate, 2011; Björkman-Nyqvist et al., 2012; MSF, 2012; Newton et al., 2011). (See Table 1-5.)

Often, the difference between a substandard and a falsified medicine is the difference between a known and unknown manufacturer. Manufacturers may produce substandard drugs because they failed to adhere to good manufacturing practices or because their internal quality systems failed. Degraded or expired products are also substandard; in some ways, failure to pull these drugs from the market is a quality system failure. Inspection of the manufacturer's records can usually distinguish between a degraded or expired drug and one that left the factory already outside of specifications.

Falsified drugs are usually also substandard. Drug regulators have no authority over underground manufacturers; nothing can be said about

The Indian generics house V.S. International's authentic ciprofloxacin (left) and a falsified version (right).
SOURCE: Bate, 2012b.

their quality controls or adherence to good manufacturing practices. It is unlikely, though not unheard of, that an illegal manufacturer would go to the trouble of making a quality-controlled medicine from quality-assured substrate.

Distinguishing between falsified and substandard drugs is a necessary first step when discussing the problem in any depth. It is admittedly something of an academic exercise, though. In many parts of the world, drugs are sold without proper packaging and emphasis on label claims has no practical value. Details of the pharmacopeial standard can also cause confusion. The U.S. Pharmacopeia, for example, gives a dissolution standard; the British Pharmacopoeia, widely used in the Commonwealth, often does not (British Pharmacopoeia, 2012b; Paleshnuik, 2009). A drug that does not dissolve is substandard nonetheless. Critics of these definitions might also point out that drug labels usually reference the pharmacopeial standard. Therefore, failing to meet the standard is also a false representation.

The definitions proposed can inevitably be caught on exceptions, but the committee believes that public discourse is best advanced by considering two main types of bad drugs: falsified and substandard. This report aims to set out useful, general terms for public discussion. Defining the products of interest is valuable only insomuch as it advances the discussion of the root causes and solutions of the problem; making definitions is not an end in itself.

Similarly, the lumping together of many competing and contradictory terms with unwieldy acronyms such as SSFFC (short for substandard, spurious, falsified, falsely labeled, and counterfeit) only encourages confusion. Speakers seeking a parent category for substandard and falsified drugs could consider illegitimate or even bad, but not SSFFC (Attaran et al., 2012).

The Problem of Unregistered Medicines

Medicines registration is one of the main responsibilities of a drugs regulatory authority (Ratanawijitrasin and Wondemagegnehu, 2002), which maintains the medicine register, "a list of all the pharmaceutical products authorized for marketing in a particular country" (WHO, 2011b, p. 43). The regulatory authority issues a market authorization, proof of entry to the medicines register, to the manufacturer of any medical product sold or distributed for free in a given country (SADC, 2007). Market authorization documents usually include the name and address of the manufacturer and information about the registered product (SADC, 2007).

Maintaining an accurate medicines register is difficult in developing countries, where the regulatory authority is often understaffed and underfunded (IOM, 2012; Ratanawijitrasin and Wondemagegnehu, 2002). To

complicate the problem, medicines travel quickly among small, landlocked countries with porous borders. The WHO found about 1,000 unregistered drugs on the Cambodian market, for example (WHO, 2003b). The amount of unregistered products on the market is also unpredictable. Sometimes bilateral trade negotiations end in large shipments of unregistered medicines in a country (Morris and Stevens, 2006; Newton et al., 2010).

In a conceptual illustration of the problem, Attaran and colleagues show that unregistered drugs may be of good quality (see Figure 1-1). This figure shows drug quality standards on the y-axis and registration on the x-axis. In this framework, drugs that fail to meet the regulatory authority's standards are divided into failures of negligence (substandard drugs) and willful failures (falsified drugs). This diagram separates the good-quality unregistered medicines from other types of illegitimate drugs. In practice, however, the distinction is not always clear.

Some research suggests that unregistered medicines can be dangerous.

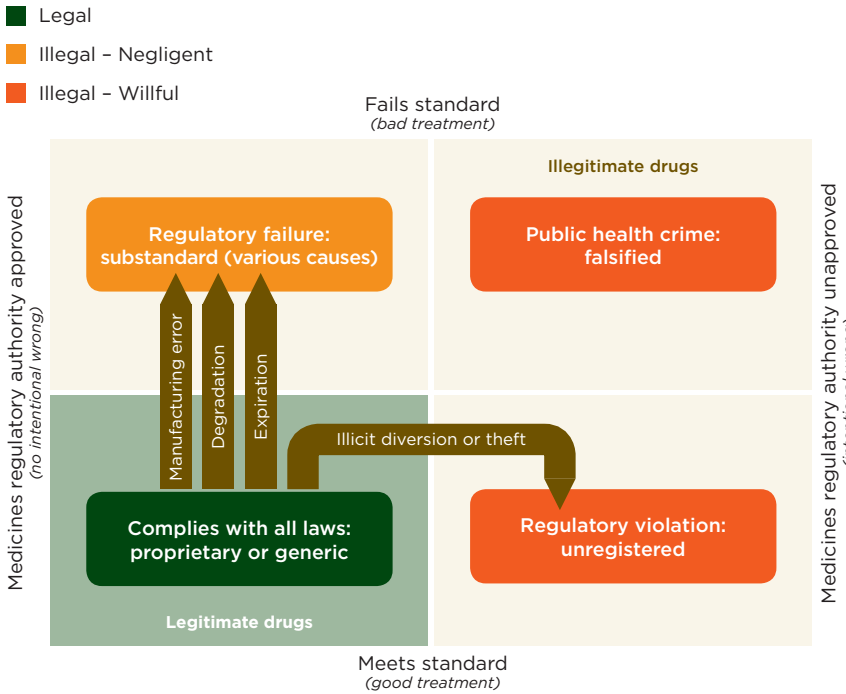

FIGURE 1-1 A two-dimensional description of medicine quality and registration.
SOURCE: Attaran et al., 2012. Reprinted with permission from BMJ Publishing Group.

A field survey of uterotonic drug quality in Ghana found that all unregistered drug samples tested were substandard; one of the unregistered products contained no active ingredient at all (Stanton et al., 2012). Many of the samples might have degraded during disorganized transport, but the explanation is never clear with unregistered drugs.

Unregistered medicines are vulnerable to quality failures. They do not enter the market through reputable channels and are often transported under poor conditions. These problems can easily go undetected. Postmarket surveillance is, by definition, a way to monitor the safety of those drugs authorized for a particular market. Therefore, the quality failures of unregistered medicines resist detection in postmarket surveillance (Amin and Snow, 2005). The proliferation of unregistered medicines suggests problems with the market authorization process in a country and, more generally, with regulatory oversight. Although unregistered drugs are not by definition falsified or substandard, they are conceptually related and part of the problem.

A Proposed Vocabulary

The lack of a consistent vocabulary has held back public discourse on the problem of poor quality medicines in the market. As Tables 1-1 through 1-5 indicate, different countries often have widely different interpretations of the same terms, creating a confusion that holds back international cooperation (Clift, 2010). Defining a common vocabulary is important, not just for this report but for all discourse on the topic.

Box 1-2 presents the definitions of the terms falsified, substandard, counterfeit, and unregistered used in this report. As this chapter explains, distinguishing between substandard and falsified medicines in the field can be difficult. In practice, there is often considerable ambiguity in real-life examples of unlabeled, poor-quality drugs. Nevertheless, falsified and substandard are good categories to describe problems with poor-quality drugs. Consistent use of these terms would ease the measuring of trends, analysis of causes, and discussion of proposed solutions to the problem.

Recommendation 1-1: The World Health Assembly should adopt definitions consistent with the following principles. Substandard drugs do not meet national specifications.[5] Falsified products have a false representation of identity or source or both. Products unregistered with the regulatory authority are also illegal.

[5] An emphasis on quality system failures is not essential to the idea of a substandard drug and was removed from the recommendation after the report release. The supporting text describes the committee's understanding of a substandard drug.

BOX 1-2
Definitions of Terms

Counterfeit: A counterfeit drug bears an unauthorized representation of a registered trademark on a product identical or similar to one for which the trademark is registered.

Falsified: A falsified drug is one that falsely represents the product's identity or source or both.

Substandard: A substandard drug is one that fails to meet national specifications cited in an accepted pharmacopeia or in the manufacturer's approved dossier.

Unregistered: An unregistered product lacks market authorization from the national regulatory authority. Though it may be of good quality, an unregistered product is illegal.

The committee agrees with the emerging consensus that falsified and substandard are the two main categories of poor-quality drugs (Bate, 2012a; Clift, 2010; MSF, 2012; Newton, 2012; Oxfam International, 2011). The World Health Assembly (WHA) is the decision-making body of the WHO (WHO, 2013) and the international authority on questions of health policy. WHA endorsement of these two main categories would advance public discourse on the topic. The spirit of the definitions, not the exact wording suggested in Box 1-2, are key to this recommendation, as is the exclusion of the term counterfeit. Counterfeit is an overly broad term and should be used only to describe trademark infringement, which is not a problem of primary concern to public health organizations. As WHO Director-General Margaret Chan explained in the opening remarks of the November 2012 member state meeting on illegitimate drugs, "trade and intellectual property considerations are explicitly excluded" from the WHO's discussions (Chan, 2012).

Falsified and substandard products are two useful categories in thinking about drug quality problems. There is overlap between these categories, but they are sufficiently precise for public discussion. Similarly, the problem of unregistered medicines is intimately linked to problems of drug quality.

DRUG QUALITY STANDARDS

The previous section mentions how national regulatory authorities set the quality standards for drugs. This section gives more detail on the history of modern medicine regulation.

Pharmacopeia

National governments have long created officially recognized lists of legal drugs. Starting in the 16th and 17th centuries, city-based pharmacopeia attempted to standardize the apothecaries' products (Brockbank, 1964). Modern pharmacopeias have been published since the 19th century: the U.S. Pharmacopeia in 1820 and the British Pharmacopoeia in 1864 (British Pharmacopoeia, 2012a; USP, 2012).

The strength of regulation by pharmacopeial standards depends on the regulatory agency to enforce the standards. In the United States, the Drug Import Act of 1848 made the U.S. Pharmacopeia the national drug compendium (USP, 2012). This recognition made the drug quality standards legally binding. In the latter half of the 19th century, state governments created licensing boards for pharmacists and pharmacies, and these boards emphasized the importance of the pharmacopeial standards (USP, 2012). The Pure Food and Drugs Act of 1906 recognized the U.S. Pharmacopeia standards as official and to be enforced by the Bureau of Chemistry in the U.S. Department of Agriculture, the forerunner of today's FDA (Swann, 2009; USP, 2012).

Terra silligata, medicinal clay from the Greek island of Lemnos (left), was stamped with a seal of authenticity (right), an early example of a drug trademark.
SOURCE: Wellcome Library, London.

The passage of the Food, Drug, and Cosmetic Act in 1938 gave the FDA new authorities and recognized the quality, packaging, and labeling standards published in the pharmacopeia and the national formulary (USP, 2012). The act also gave the FDA inspectorate the authority to enforce these standards (USP, 2012). The 1960s saw several changes to accepted drug regulation, including the creation of an Adopted Names Council, an organization that establishes the United States Adopted Names, unique nonproprietary names for drugs (AMA, 2012; USP, 2012). Eventually the U.S. Pharmacopeia purchased the National Formulary and Drug Standards Laboratory from the American Pharmacists' Association (USP, 2012). They merged the formulary and pharmacopeia in 1975, creating a collection of more than 4,000 monographs (USP, 2008).

Around the same time in Europe, the unified economic community was encouraging the use of regional pharmacopeial standards (EDQM, 2012). The first official European pharmacopeia was published in 1964 and is currently in its seventh edition (EDQM, 2012; *European Pharmacopoeia*, 2012). The European Directorate for the Quality of Medicines maintains and revises the *European Pharmacopoeia* and runs chemical and biological laboratories devoted to testing pharmaceutical products intended for the EU market (EDQM, 2012). While the FDA enforces pharmacopeial standards in the United States, both the national regulatory authorities and the European Directorate enforce the pharmacopeial standards in Europe (AVMA, 2012; EDQM, 2012). The European Medicines Agency (EMA), often described as the counterpart of the FDA, is primarily a medicines registration (review and approval) agency. The European Directorate has more responsibility for enforcing quality standards (EDQM, 2012).

In China and India, national pharmacopeial standards and organizations have developed rapidly in the last two decades. The government of India began enforcing pharmaceutical standards more systematically after the Drugs and Cosmetics Act of 1940 (Gothoskar, 1983). Only in 2009, however, did the Indian Pharmacopoeia Commission became an independent agency under the Ministry of Health, separate from the drug regulatory authority (Indian Pharmacopoeia Commission, 2011). The Indian government also maintains a pharmacopeia on ayurvedic medicines, first published in a single volume in 1978 (Pharmacopoeial Laboratory for Indian Medicine, 2011).

Registration Agencies and National Pharmaceutical Authorities

National regulatory authorities are responsible for approving new drugs, also known as drug registration or medicines licensing (Rägo and Santoso, 2008). These agencies conduct the premarket safety and effi-

cacy reviews. They also conduct inspections and enforce quality control regulations.

The USDA Bureau of Chemistry was the forerunner of the FDA and one of the first agencies dedicated to quality enforcement for food and drugs (FDA, 2010). This agency enforced drug quality and antiadulteration standards in accordance with the Pure Food and Drugs Act of 1906. In 1927 it became a separate agency in the Department of Agriculture (Swann, 2009). Premarket review for drugs was not part of the drug registration process in the United States until the Federal Food, Drug, and Cosmetic Act of 1938, though premarket authorization of vaccines was mandatory after 1902 (FDA, 2012c).

The development of national registration entered a new phase in the two decades following World War II. In the 1940s and 1950s, before the thalidomide crisis of the early 1960s, federal drug regulators in the United States began to regulate efficacy (Carpenter, 2010; FDA, 2012c). In 1958, the Netherlands Medicines Act created an advanced administrative drug registration system and established, but did not yet use, the Medicines Evaluation Board to regulate market approval of new drugs (Carpenter, 2010; MSH, 2012).

The global thalidomide tragedy in the early 1960s changed all these institutions. Thalidomide was a sedative and antiemetic developed in Germany, used widely throughout Australia, Europe, and Japan in the late 1950s (Kim and Scialli, 2011). It was effective against morning sickness and commonly prescribed to pregnant women (Bren, 2001; Kim and Scialli, 2011). By 1961, however, thalidomide was identified as the cause of severe birth defects in more than 10,000 children. Birth defects included abnormally short limbs, toes sprouting directly from the hips, flipper-like arms, or no limbs at all; eye and ear defects; and congenital heart disease (Bren, 2001; Kim and Scialli, 2011). The drug was pulled from the market in 1961 and 1962 (Fintel et al., 2009; Kim and Scialli, 2011). Thalidomide had been licensed in 46 countries, but in the United States, the FDA had refused to approve its application and the drug never entered the market (Bren, 2001).

After the tragedy, governments worldwide revamped their drug regulation systems. The Drug Amendments of 1962 officially added efficacy to safety as a basis for FDA regulation and as a necessity for marketing authorization in the United States and imposed clinical trial requirements on drug development (FDA, 2012b). Australia, Britain, and Germany changed their systems of drug regulation in 1963 and 1964 (Daermmrich, 2003; Rägo and Santoso, 2008; TGA, 2003). Following the European Economic Community resolutions in 1965 and the 1970s, Britain, France, Germany, and other European nations took further steps to build stronger, more scientific regulatory agencies based in part upon the FDA model (Carpenter, 2010; ECHAMP, 2012). Hence, although thalidomide was not a problem of

substandard or falsified drugs, the reforms in its wake profoundly affected drug registration and quality control around the world.

Good manufacturing practices and bioequivalence standards, in addition to traditional pharmacopeial standards, are two of the most important conceptual instruments of modern drug quality regulation. Good manufacturing practices issued from the 1938 Federal Food, Drug, and Cosmetic Act's stipulation that if "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such [new] drugs are inadequate to preserve its identity, strength, quality and purity," the FDA would reject the new drug application.[6] After the 1941 sulfathiazole disaster, FDA officials strengthened inspection protocols, requiring manufacturers not simply to prove drug quality but to demonstrate and maintain practices that assured uniformly standard drugs as well. Good manufacturing practices have now been adopted worldwide and are used not only by national regulatory authorities but also by pharmacopeial organizations like the EDQM, international health organizations like the WHO, and the International Conference on Harmonisation. They are applied to traditional medicines as well as to allopathic drugs (Carpenter, 2010).

The rise of generic drugs in the 20th century raised new questions about bioequivalence. From the 1950s to the late 1970s, bioequivalence standards, which required measuring metabolites in urine and blood, replaced older standards of chemical equivalence, which required only laboratory and dissolution tests (Carpenter and Tobbell, 2011). Between 1973 and 1977, the FDA issued bioequivalence rules and, in 1979, published a book of therapeutically equivalent products. These rules, coupled with the Hatch-Waxman Act of 1984, cemented a new generic drug approval process and bioequivalence regulations (Carpenter and Tobbell, 2011).

[6] The Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(d)(3)(2012).

TABLE 1–1 Definitions of Counterfeit Pharmaceuticals

Organization	Definition	
WHO	**1992**	"A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with correct ingredients, wrong ingredients, without active ingredients, with insufficient quantity of active ingredient or with fake packaging" (WHO, 1992, p. 1).
	2003	"Counterfeit medicines are part of the broader phenomenon of substandard pharmaceuticals. The difference is that they are deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients" (WHO, 2003a).
	2006	"Counterfeit medicines are part of the broader phenomenon of substandard pharmaceuticals. . . . They are deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients" (WHO, 2006).
	2009	"A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging" (WHO, 2009).
	2011	Never explicitly defined, except as part of the so-called spurious, substandard, falsified, falsely labeled, counterfeit (SFFC). "There are no good quality SSFC medicines. By definition SSFC medicines are products whose true identify and/or source are unknown or hidden. They are mislabeled . . . and produced by criminals" (WHO, 2011a).

IMPACT	**2008**	"The term counterfeit medical product describes a product with a false representation (a) of its identity (b) and/or source (c). This applies to the product, its container or other packaging or labeling information. Counterfeiting can apply to both branded and generic products. Counterfeits may include products with correct ingredients/components (d), with wrong ingredients/components, without active ingredients, with incorrect amounts of active ingredients, or with fake packaging. Violations or disputes concerning patents must not be confused with counterfeiting of medical products. Medical products (whether generic or branded) that are not authorized for marketing in a given country but authorized elsewhere are not considered counterfeit. Substandard batches of, or quality defects or non-compliance with Good Manufacturing Practices/Good Distribution Practices (GMPs/GDPs) in legitimate medical products must not be confused with counterfeiting. Notes: a) Counterfeiting is done fraudulently and deliberately. The criminal intent and/or careless behavior shall be considered during the legal procedures for the purposes of sanctions imposed. b) This includes any misleading statement with respect to name, composition, strength, or other elements. c) This includes any misleading statement with respect to manufacturer, country of manufacturing, country of origin, marketing authorization holder or steps of distribution. d) This refers to all components of a medical product" (IMPACT, 2008).
Oxfam	A medicine that infringes on a trademark (Brant and Malpani, 2011).	
World Trade Organization	"Unauthorized representation of a registered trademark carried on goods identical or similar to goods for which the trademark is registered, with a view to deceiving the purchaser into believing that he/she is buying the original goods" (WTO, 2012).	
World Bank	"Counterfeits are usually defined as drugs that are deliberately made as fake copies of the original branded or generic drugs, imitating design, colors and other visible features. In many cases they contain only filling materials without any active ingredients. Or they may contain insufficient or an excess of active ingredients, or active drug substances other than the ones specified in the label" (Siter, 2005).	
World Medical Association	"Counterfeit medicines are drugs manufactured below established standards of safety, quality and efficacy and therefore create serious health risks, including death" (WMA, 2012).	

continued

TABLE 1–1 *Continued*

Organization	Definition
TRIPS Agreement	"[Counterfeit trademark goods] shall mean any goods, including packaging, bearing without authorization a trademark which is identical to the trademark validly registered in respect of such goods, or which cannot be distinguished in its essential aspects from such a trademark, and which thereby infringes the rights of the owner of the trademark in question under the law of the country of importation" (WTO, 1994).
Doctors Without Borders	"Counterfeit medicines are products that are presented in such a way as to look like a legitimate product although they are not that product. In legal terms this is called trademark infringement. They are the result of deliberate criminal activity that has nothing to do with legitimate pharmaceutical producers—be it generic or brand producers" (MSF, 2009).
Pharmaceutical Security Institute	Counterfeit medicines are products deliberately and fraudulently produced and/or mislabeled with respect to identify and/or source to make it appear to be a genuine product. This applies to both branded and generic products. They can have more or less than the required amount of active pharmaceutical ingredients (APIs) or have the correct amount of API, but manufactured in unsanitary, unsafe conditions. This definition can also be extended to genuine medicines. Genuine medicines can be placed in counterfeit packaging to extend its expiry date (PSI-Inc., 2012).
The Partnership for Safe Medicines	"Counterfeit drugs are fake medicines intentionally made by unknown manufacturers who hide their identity. These drugs do not meet established standards of quality. Counterfeit drugs deceive consumers by closely resembling the looks of a genuine drug. They are made without approval of the regulator, such as the U.S. Food and Drug Administration (FDA). Counterfeiters create fake versions of branded, generic and over-the-counter drugs. Counterfeit medicines have been found to be made missing key ingredients; too strong or too weak; with the wrong active ingredient; with dangerous contaminants; in unsanitary or unsterile conditions; using unsafe methods; and with improper labels" (PSM, 2012).
International Pharmaceutical Federation	"Counterfeiting in relation to medicinal products means the deliberate and fraudulent mislabeling with respect to the identity, composition and/or source of a finished medicinal product, or ingredient for the preparation of a medicinal product. Counterfeiting can apply to both branded and generic products and to traditional remedies. Counterfeit products may include products with the correct ingredients, wrong ingredients, without active ingredients, with insufficient quantity of active ingredient or with false or misleading packing; they may also contain different, or different quantities of, impurities both harmless and toxic" (FIP, 2003).
International Federation of Pharmaceutical Manufacturers and Associations	"Counterfeit medicines threaten the full spectrum of legitimate medicines. They can be falsified versions of patented medicines, generic medicines or over-the-counter medicines and exist in all therapeutic areas (even traditional medicine). They range from medicines with no active ingredients to those with dangerous adulterations" (IFPMA, 2010).

TABLE 1–2 National Definitions of Counterfeit Pharmaceuticals

Country	Definition	
Cambodia	"A counterfeit pharmaceutical product is a medicine: 1. which is deliberately produced with the incorrect quantity of active ingredients or wrong active ingredients, or 2. a medicine that is either without active ingredients, or with amounts of active ingredients that are deliberately outside the accepted standard as defined in standard pharmacopoeias, or 3. a medicine that is deliberately and fraudulently mislabeled with respect to identity and/or source, or one with fake packaging, or 4. a medicine that is repacked or produced by an unauthorized person" (Phana, 2007).	
United States	**Food, Drug, and Cosmetic Act**	"A drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor."[a]
	U.S. Food and Drug Administration Website	"Counterfeit medicine is fake medicine. It may be contaminated or contain the wrong or no active ingredient. They could have the right active ingredient but at the wrong dose. Counterfeit drugs are illegal and may be harmful to your health" (FDA, 2012a).
	United States Code	Having a spurious trademark, not genuine or authentic, identical with, or substantially indistinguishable from the genuine trademark, registered on the principal register in the U.S. Patent and Trademark Office and in use. The counterfeit mark is likely to cause confusion, to cause mistakes, or to deceive. [general trademark counterfeit][b]

continued

TABLE 1–2 *Continued*

Country	Definition	
China	**Drug Administration Law of the People's Republic of China**	"A drug is a counterfeit drug in any of the following cases: 1. the ingredients in the drug are different from those specified by the national drug standards; or 2. a non-drug substance is simulated as a drug or one drug is simulated as another. A drug shall be treated as a counterfeit drug in any of the following cases: 1. its use is prohibited by the regulations of the drug regulatory department under the State Council; 2. it is produced or imported without approval, or marketed without being tested, as required by this Law; 3. it is deteriorated; 4. it is contaminated; 5. it is produced by using drug substances without approval number as required by this Law; or 6. the indications or functions indicated are beyond the specified scope."[c]
Philippines	"Medicinal products with correct ingredients but not in the amounts as provided there under, wrong ingredients, without active ingredients, with insufficient quantity of active ingredients, which results in the reduction of the drug's safety, efficacy, quality, strength, or purity. It is a drug which is deliberately and fraudulently mislabeled with respect to identity and/or source or with fake packaging and can apply to both branded and generic products. It shall also refer to: 1) the drug itself, or the container or labeling thereof or any part of such drug, container, or labeling bearing without authorization the trademark, trade name, or other identification mark or imprint or any likeness to that which is owned or registered in the Bureau of Patent, Trademark, and Technology transfer in the name of another natural or juridical person; 2) a drug product refilled in containers by unauthorized persons if the legitimate labels or marks are used; 3) an unregistered imported drug product, except drugs brought in the country for personal us as confirmed and justified by accompanying medical records; and 4) a drug which contains no amount of or a different active ingredient, or less than 80% of the active ingredient it purports to possess, as distinguished from an adulterated drug including reduction or loss of efficacy due to expiration" (Clift, 2010, p. 15).	
Pakistan	"A drug, the label or outer packaging of which is an imitation of, resembles as to be calculated to deceive, the label or outer packing of a drug manufacturer" (Clift, 2010, p. 15).	

Nigeria	"a) Any drug product which is not what it purports to be; or b) any drug or drug product which is so colored, coated, powdered or polished that the damage is concealed or which is made to appear to be better or of greater therapeutic value than it really is, which is not labeled in the prescribed manner or which label or container or anything accompanying the drug bears any statement, design, or device which makes a false claim for the drug which is false or misleading; or c) any drug or drug product whose container is so made, formed or filled as to be misleading; or d) any drug product whose label does not bear adequate directions for use and such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health or against unsafe dosage or methods or duration of use; or e) any drug product which is not registered by the Agency in accordance with the provisions of the Food, Drugs and Products (Registration, etc.) Decree 1993, as amended" (Clift, 2010, p. 15).	
India	**Mashelkar Report**	"The term, 'counterfeit' that is commonly used worldwide for spurious drugs does not appear in Drugs and Cosmetic Act but the definition of spurious drug comprehensively covers counterfeit drugs. According to the Drugs and Cosmetic Act (by the Amendment Act of 1982, section 17-B) spurious drugs are: a) manufactured under a name which belongs to another drug; or b) an intimation of, or a substitute for, another drug or resembles another drug in a manner likely to deceive or bear upon it or upon its label or container the name of another drug unless it is plainly and conspicuously marked so as to reveal its true character and its lack of identity with such other drug; or c) labeled or in a container bearing the name of an individual or company purporting to be the manufacturer of the drug, which individual or company is fictitious or does not exist; or d) substituted wholly or in part by another drug or substance; or e) purporting to be the product of a manufacturer of whom it is not truly a product" (Government of India, 2003).

continued

TABLE 1-2 *Continued*

Country	Definition	
Indonesia	**2000**	Per the Republic of Indonesia's Ministry of Health (MOH) Regulation No. 242/2000, counterfeit medicine(s) is/are the medicine(s) that are produced by the party/parties who has/have no authority to produce it based on the government's act. There are five kinds of counterfeit medicines: 1. Product containing API with required concentrations; produced, packaged, and labeled as the original product, but this product is produced by the party without license. 2. The medicine contains API, but the concentration is outside of requirements. 3. Product is made as the original form and package, but no content of API. 4. The product is similar to the original, but content is of different substances/materials. 5. Products that are produced without a permit from the MOH. Per Republic Indonesian MOH Regulation No. 949/MenKes/SK/VI/2000 imported product/s that are illegal can be grouped as counterfeit without a permit for circulation issued by the National Agency of Food and Drug Control.
	2008	Per the republic of Indonesia's Regulation No. 1010/2008, counterfeit medicines are produced by the party/ies who has/have no authority to produce the medicines by the government's act, or medicines whose identities are imitated by other medicines that already have a circulating permit. There are three categories of counterfeit medicine: 1. The volume of substance (API) and the trade name is the same as the original medicine, but produced by the party who has no license to produce it. 2. The trade name is the same as the original medicine, but the volume of substance (API) is different and produced by the other producer. 3. The trade name is the same as the original, but the content of substance (API) is not medicine and not clear how the processing produced the drug.

Kenya	**2008 Anti-Counterfeit Bill**	"'Counterfeiting' means taking the following actions without the authority of the owner of any intellectual property right subsisting in Kenya or elsewhere in respect of protected goods— a) the manufacture, production, packaging, re-packaging, labeling or making, whether in Kenya or elsewhere, of any goods whereby those protected goods are imitated in such manner and to such a degree that those other goods are identical or substantially similar copies of the protected goods; b) the manufacture, production or making, whether in Kenya or elsewhere, the subject matter of that intellectual property, or a colorable imitation thereof so that the other goods are calculated to be confused with or to be taken as being the protected goods of the said owner or any goods manufactured, produced or made under his license; c) the manufacturing, producing or making of copies, in Kenya or elsewhere, in violation of an author's rights or related rights."[d]
Mexico	It is considered a *falsificado* product when it is manufactured, packaged, or sold with reference to an authorization that does not exist, or uses a permit granted by law to another or imitation of legally manufactured and registered products.[e]	
Europe	**Council of Europe**	A false representation as regards identity and/or source (Council of Europe, 2011).
	European Medicines Agency	"Counterfeit medicines are medicines that do not comply with intellectual-property rights or that infringe trademark law" (EMA, 2012).
Vietnam	"Counterfeit drugs mean products manufactured in any form of drug with a deceitful intention, and falling into one of the following cases: a) they have no pharmaceutical ingredients; b) they have pharmaceutical ingredients, which are, however, not at registered contents; c) they have pharmaceutical ingredients different from those listed in their labels; d) they imitate names and industrial designs of drugs which have been registered for industrial property protection of other manufacturing establishments."[f]	

[a] Federal Food, Drug, and Cosmetic Act. As amended December 19, 2002. Chap. II, Sec. 201, (g)(2).

[b] 18 U.S.C. § 2320. (f)(1). (2012).

[c] *Drug Administration Law of the People's Republic of China*. (China). 2001. Chap. V, Art. 48.

[d] The Anti-Counterfeit Bill, 2008. (Kenya). Part I, 2 (a-c).

[e] Ley General de Salud. (Mexico). 2013. Tit. 1, Chap. 1, Art. 208 bis.

[f] Law on Pharmacy. (Vietnam). 2005. Chap. 1, Art. 2. (24).

TABLE 1–3 Definitions of Substandard Pharmaceuticals

Organization	Definition	
World Health Organization	**2003**	"Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications and which are consequently ineffective and often dangerous to the patient. Substandard products may occur as a result of negligence, human error, insufficient human and financial resources or counterfeiting" (WHO, 2003a).
	2006	"Substandard pharmaceuticals [are] medicines manufactured below established standards of safety, quality and efficacy" (WHO, 2006).
	2009	"Substandard medicines (also called out of specification [OOS] products) are genuine medicines produced by manufacturers authorized by the [national medicines regulatory authority] which do not meet quality specifications set for them by national standards" (WHO, 2009).
	2010	"Each pharmaceutical product that a manufacturer produces has to comply with quality standards and specifications at release and throughout the product shelf-life required by the territory of use. Normally, these standards and specifications are reviewed, assessed and approved by the applicable national medicines regulatory authority before the product is authorized for marketing. Substandard medicines are pharmaceutical products that do not meet their quality standards and specifications" (WHO, 2010).
	2011	Substandard medicines are pharmaceutical products that do not meet their quality standards and specifications. "They arise mostly due to the application of poor manufacturing practices by the producer or when a good quality medicine is stored and distributed under improper conditions leading to deterioration of the quality of the product" (WHO, 2011a).
Oxfam	"Substandard medicines do not meet the scientific specifications for the product as laid down in the WHO standards. They may contain the wrong type or concentration of active ingredient, or they may have deteriorated during distribution in the supply chain and thus become ineffective or dangerous" (Brant and Malpani, 2011).	
The Partnership for Safe Medicines	"Substandard drugs are produced by a known manufacturer, but they do not meet the quality standards of the drug regulator. In the United States, these high standards are set by the United States Pharmacopeia and the National Formulary. There is no intent to fool or defraud the consumer. Substandard medications are a result of manufacturer that do not follow approved Good Manufacturing Practices, which is regulated by the FDA. Simply stated, these drugs fall below the established standard—hence the term 'substandard drugs'" (PSM, 2012).	

U.S. Pharmacopeia	"Substandard drugs can be found in a variety of forms. A substandard product is a legally branded or generic product, but one that does not meet international standards for quality, purity, strength, or packaging. To be considered 'substandard' a product could: • Contain no active ingredient, but harmless inactives; • Contain harmful or poisonous substances; • Not be registered, or have been manufactured clandestinely, or smuggled into the country and thus be on sale illegally; • Have been registered inadvisably by a weak agency; or • Have passed its expiration date" (Smine, 2002, p. 1).
World Bank	"Substandard drugs are manufactured with the intent of making a genuine pharmaceutical product, but the manufacturer saves costs by not following GMP (Good Manufacturing Practice) or using poor quality raw materials. Another potential problem relates to inadequate storage or transport conditions, leading to deterioration of the product. The performance of such medicines is questionable." (Siter, 2005).
International Federation of Pharmaceutical Manufacturers and Associations	"All substandards are not counterfeits. A medicine which is approved and legally manufactured but does not meet all quality criteria is substandard, and may pose a significant health risk, but should not be regarded as counterfeit. However, all counterfeits are, by their nature, at high risk of being substandard" (IFPMA, 2010).

TABLE 1–4 National Definitions of Substandard Pharmaceuticals

Country	Definition
Cambodia	A substandard drug is a registered product, whose specifications are outside of accepted standards as defined by reference pharmacopoeias (Phana, 2007).
China	"A drug with content not up to the national drug standards is a substandard drug. A drug shall be treated as a substandard drug in any of the following cases: 1. the date of expiry is not indicated or is altered; 2. the batch number is not indicated or is altered; 3. it is beyond the date of expiry; 4. no approval is obtained for the immediate packaging material or container; 5. colorants, preservatives, spices, flavorings or other excipients are added without authorization; or 6. other cases where the drug standard are not conformed."[a]
Philippines	"Substandard product means the product fails to comply, with an applicable risk of injury to the public."[b]
Thailand	Substandard drugs are: "1. Drugs produced with active substances which quantity or strength are lower than the minimum or higher than the maximum standards prescribed in the registered formula to a degree less than the stated in Section 73 (5) [of the Thai Drug Act of 1967]. 2. Drugs produced so that their purity or other characteristics which are important to their quality differ from the standards prescribed in the registered formula under Section 79 or drug formulas which the Minister has ordered the drug formula registry under Section 86 bis [of the Thai Drug Act of 1967]."[c]

[a] Drug Administration Law of the People's Republic of China. (China). 2001. Chap. V, Art. 49.

[b] Republic Act No. 7394, The Consumer Act of the Philippines. (Philippines). Tit. I, Art. 4 (bt).

[c] Thailand Drug Act, B.E. 2510 (1967). (Thailand). Chap. VIII, Sec. 74.

TABLE 1–5 Other Terms of Interest

Organization	Term	Definition
Oxfam	**Falsified**	Medicines for which the identity, source, or history was misrepresented (parent category for fake and falsely labeled) (Brant and Malpani, 2011).
	Falsely labeled	The true properties of the product do not correspond to the information provided (Brant and Malpani, 2011).
	Fake	Does not contain the correct type of concentration of active and/or other ingredients (Brant and Malpani, 2011).
European Medicines Agency	**Falsified**	"Falsified medicines are fake medicines that pass themselves off as real, authorized medicines. Falsified medicines may: • contain ingredients of low quality or in the wrong doses; • be deliberately and fraudulently mislabeled with respect to their identity or source; • have fake packaging, the wrong ingredients, or low levels of the active ingredients. Falsified medicines do not pass through the usual evaluation of quality, safety and efficacy, which is required for the European Union (EU) authorization procedure. Because of this, they can be a health threat" (EMA, 2012).
Brazil	**Falsification of medicines**	"Illicit reproduction of registered medicine, made by [a] third [party], with the fraudulent intention of giving a legitimate appearance of what is not legitimate" (Anvisa, 2006).
	Adulteration	"Intervention of [a] third [party], with the purpose of altering legitimate medicine in [a] way to commit therapeutic effectiveness and/or to turn it noxious to the health; or intervention that modifies the specifications of the registration fraudulently, changing its registered formulation" (Anvisa, 2006).
	Alteration	"Modification for addition or subtraction of components of the medicine and/or if the pharmaceutical formula, without previous and expressed approval of the National Agency of Health Surveillance" (Anvisa, 2006).

continued

TABLE 1–5 *Continued*

Organization	Term	Definition
Council of the European Union	**Falsified**	"Falsified medicinal product [is] any medicinal product with a false representation of: a) its identity, including its packaging and labeling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder; or c) its history, including the records and documents relating to the distribution channels used. This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights."[a]
Thailand	**Deteriorated Drugs**	The following are deteriorated drugs: "1. A drug the expiry date of which as shown on the label has been reached. 2. A drug which has so denatured as to have the characteristics of a fake drug."[b]
	Fake	The following drugs or substances are fake drugs: "1. A drug or substance which is wholly or partly an imitation of a genuine drug; 2. A drug which shows the name of another drug, or an expiry date which is false; 3. A drug which shows a name or mark of a producer, or the location of the producer [of] the drug, which is false; 4. Drugs which falsely show that they are in accordance with a formula which has been registered; and 5. Drugs produced with active substances which quantity or strength [is] lower than the minimum or higher than the maximum standards prescribed in the registered formula by more than twenty percent."[c]
India	**Misbranded**	"A drug shall be deemed to be misbranded— a) if it is so colored, coated, powdered or polished that damage is concealed or if it is made to appear of better or greater therapeutic value than it really is; or b) if it is not labeled in the prescribed manner; or c) if its label or container or anything accompanying the drug bears any statement, design or device which makes any false claim for the drug or which is false or misleading in any particular."[d]

Adulterated	"A drug shall be deemed to be adulterated— a) if it consists, in whole or in part, of any filthy, putrid or decomposed substance; or b) if it has been prepared, packed or stored under insanitary conditions whereby it may have been contaminated with filth or whereby it may have been rendered injurious to health; or c) if its container is composed in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or d) if it bears or contains, for purposes of coloring only, a color other than one which is prescribed; or e) if it contains any harmful or toxic substance which may render it injurious to health; or f) if any substance has been mixed therewith so as to reduce its quality or strength."[e]

[a] Directive 2011/62/EU on the community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products [2011] OJ L174/77-78.

[b] Thailand Drug Act, B.E. 2510 (1967). (Thailand). Chap. VII, Sec. 75.

[c] Thailand Drug Act, B.E. 2510 (1967). (Thailand). Chap. VII, Sec. 73.

[d] The Drugs and Cosmetics Act and Rules. (India). As corrected up to 30th April, 2003. Chap. III, 9C.

[e] The Drugs and Cosmetics Act and Rules. (India). As corrected up to 30th April, 2003. Chap. III, 9A.

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2

The Effects of Falsified and Substandard Drugs

A safe medicines supply is fundamental for public health. This chapter describes consequences of falsified and substandard drugs. Drawing on a range of examples from both academic literature and other sources, it discusses the relationships between drug failure and health problems at the individual and population levels. The chapter does not attempt to present an exhaustive analysis of every health consequence of substandard or falsified drugs, but it gives an overview of the kinds of health problems these products cause. The second section of this chapter analyzes the economic and social costs of a substandard drug supply, including loss of confidence in the health care system.

PUBLIC HEALTH CONSEQUENCES

A reliable, good-quality medicine supply is essential for health, but it is often missing in countries with weak regulatory systems (Ratanawijitrasin and Wondemagegnehu, 2002). The fallout of falsified and substandard medicines includes poisoning, untreated disease, early death, and treatment failure.

Poisoning

Some of the most compelling stories of pharmaceutical fraud are those of frank poisoning. Between November 2008 and February 2009, 84 Nigerian children died from acute kidney failure brought on by the industrial solvent diethylene glycol in teething syrup (Akuse et al., 2012;

Key Findings and Conclusions

- Falsified and substandard drugs may contain toxic doses of dangerous ingredients and cause mass poisoning.
- Poor-quality medicines compromise the treatment of chronic and infectious diseases, causing disease progression, drug resistance, and death.
- As chronic diseases increase in low- and middle-income countries, so will the need for reliable medicines.
- Substandard and falsified medicines encourage drug resistance, threatening the health of populations today and in the future.

Polgreen, 2009). The contaminated product, My Pikin, was registered with the Nigerian regulatory authority and made in Lagos, the national manufacturing hub (Akuse et al., 2012). Inspectors traced the problem back to deliberate fraud by a chemical dealer in Lagos, eventually leading to 12 prosecutions (Poisoned teething drug arrests, 2009; Polgreen, 2009).

A similar tragedy unfolded on a larger scale the previous year in Panama when a Chinese chemical manufacturer sold diethylene glycol, the active ingredient in antifreeze, as pharmaceutical-grade glycerin to a European company (Bogdanich and Hooker, 2007). The poison caused acute kidney failure in the people who ingested it, often as the solvent in cough syrup (Bogdanich and Hooker, 2007; CDC, 2009). The Panamanian government counted 219 deaths from kidney failure brought on by diethylene glycol poisoning (Núñez, 2011). Given that more than 60,000 bottles of cough syrup and some lotions were contaminated, the Ministry of Health and the World Health Organization (WHO) assume that these confirmed deaths are probably only a fraction of the total mortality (Rentz et al., 2008).

The 2006 diethylene glycol poisoning was an international tragedy, and 18 of the causalities were Chinese (Bogdanich, 2007). In the early 2000s some sources called China "the world's largest producer of bogus medicines"; Chinese newspaper accounts contain stories of similar mass poisonings (Fackler, 2002). In 2001 reporters described the death of a southwest China mine owner from a poisoned albumin drip (Fackler, 2002). A decade later, the Chinese State Food and Drug Administration (SFDA) found that 13 percent of capsule manufacturers are making drugs containing unsafe levels of chromium, a toxic metal (Rickman, 2012). The SFDA identified 254 separate companies as sources of the chromium-tainted medicines (Rickman, 2012).

Though poisonous drugs are part of the story, the more insidious

problem is medicine that simply does not work. Ineffective medicines often contain benign ingredients, such as chalk, pollen, or flour, instead of medicinal chemicals. More dangerously, some contain substances intended to mask the illness and feign treatment, such as paracetemol added to fake antimalarials to lower fever. Patients taking ineffective drugs die of apparently natural causes, making these products more difficult to identify.

Untreated Disease, Disease Progression, and Death

Medicine is intended to cure patients, or at least to relieve symptoms or slow the progression of a disease. There is also useful information in treatment failure. When prescribing medicines of known content and potency, the clinician may suspect inadequate dosing, drug resistance, or misdiagnosis if the patient does not respond to treatment as expected. These inferences are central to the practice of medicine. The Partnership for Safe Medicines, an American nonprofit, encourages doctors to suspect counterfeit[1] drugs in cases of treatment failure (PSM, n.d.), but there is little published evidence to suggest they do so. Advising physicians to consider the possibility of medicine fraud suggests that they have a way to verify it. In parts of the world where such assays are too costly or too technologically complicated to pursue, this information is usually unknowable. Confirmed accounts of drug failure are only a fraction of the larger, mostly invisible, problem.

Research at the medicine store can help illuminate these problems. A random sample of all known medicine shops in three districts of Ghana found the uterotonic drugs oxytocin and ergometrine to be of uniformly poor quality: 89 percent of the samples tested were below British Pharmacopoeia specifications though only 2 percent were expired (Stanton et al., 2012). Unicef, the United Nations Children's Fund, estimates the maternal mortality ratio in Ghana to be 350 per 100,000 live births (Unicef, 2003), of which hemorrhage, a condition treated with uterotonic drugs, is the most common cause (Asamoah et al., 2011). Even in Ghanaian hospital studies, where one would expect hemorrhage to be an uncommon cause of death, it accounts for an estimated 17 to 22 percent of maternal deaths (Ganyaglo and Hill, 2012; Lee et al., 2012). Increasing access to emergency obstetric care is a key piece of any strategy to reduce maternal mortality (Campbell and Graham, 2006), one that lies on the assumption that lifesaving uterotonic medicines are of reliable potency. Research suggests they are not, even in a middle-income country like Ghana.

The type of study Stanton and colleagues undertook in Ghana is rare.

[1] The Partnership for Safe Medicines uses the term *counterfeit* broadly, the way this report uses *falsified*. See page 23.

They were able to draw conclusions about uterotonic drug quality because their data represented a random sample of drugs from an almost exhaustive sampling frame of known pharmacies, chemical shops, and other dispensaries in their study area (Stanton et al., 2012). The identification of falsified and substandard medicines is more often incidental, found in newspaper accounts or uncovered in research that had a different primary aim.

Medications for Chronic Diseases

In 2009 a southwest China newspaper reported on a substandard version of the diabetes drug glibenclamide (also called glyburide) found to contain six times the pharmacopeial standard dose (Xiang, 2009). The medicine was tested only after killing two people and injuring nine (Cheng, 2009; Xiang, 2009). Like oxytocin and ergometrine, glibenclamide is a WHO essential medicine, as is only one other oral diabetes drug, metformin (WHO, 2011c). Metformin too has been the subject of quality concerns. In a convenience sample of pharmacies in Lagos, Nigeria, researchers found that four of eight popular brands of metformin tablets failed one or more pharmacopeial tests of bioequivalence (Olusola et al., 2012). These are troubling findings, given that an estimated 80 percent of the world's 347 million diabetics live in low- and middle-income countries, where medicines quality is most variable, and diabetes case-fatality exorbitantly high (Unachukwu et al., 2008; WHO, 2011a). Dora Akunyili, the former director of the Nigerian drug regulatory authority, worked against pharmaceutical fraud, a cause she committed to after her diabetic sister's death from fake insulin (Cheng, 2009; Lemonick, 2005).

Medication for other chronic diseases has been compromised in developing countries. A Rwandan study on drug stability found that 20 percent of medicines in a sample of Kigali and Butare pharmacies were substandard at the time of purchase (Twagirumukiza et al., 2009). Two studies of the antihypertensive amlodipine's quality in south Nigeria found problems: one study reported 30 percent of samples failed pharmacopeial tests for content uniformity (Eichie et al., 2011) and, in another, all samples failed (Olajide et al., 2010). The management of diseases such as type 2 diabetes and hypertension depend on maintenance medication and monitoring. The sheer amount of products used to treat these conditions raises the patients' lifetime risk of encountering a bad product, even in countries with stringent regulatory authorities (see Box 2-1). The need for reliable medicines in low- and middle-income countries will become more pronounced as the burden of chronic disease increases in these countries. Already cardiovascular disease is the main killer of adults in low- and middle-income countries,

BOX 2-1
Defective Glucose Test Strips

In October 2006, the FDA recalled two batches of blood glucose test strips used in LifeScan, Inc. OneTouch Ultra brand blood glucose monitors after LifeScan notified the agency that it had received a number of customer complaints. The strips produced inaccurate blood glucose level readings, the results of which are used by diabetics to monitor their condition and determine medication dosing (Bloomberg News, 2007). Diabetics rely on their blood glucose monitors to manage their self-treatment, and incorrect readings can lead patients to administer the wrong dosage of insulin or induce unnecessary panic. Improper insulin dosing is a potentially fatal error. In the LifeScan recall, the FDA identified the problem strips and instructed consumers to inspect the serial numbers on their boxes and replace any fake or unidentifiable strips (FDA, 2006; WHO, 2006).

Investigation traced the strips back to Halson Pharmaceuticals in Shanghai. The manufacturer sold approximately one million substandard test strips to importers, and from there the strips went through the supply chain to reach U.S. and Canadian pharmacies. Over the course of the next year, the test strips made their way to 8 countries and 35 U.S. states. The Chinese authorities eventually arrested and imprisoned Henry Fu, owner of Halson Pharmaceuticals (Bloomberg News, 2007).

The LifeScan recall is a reminder that substandard medical products can find their way into countries with strong regulatory systems. The United States and Canada have systems in place for prompt recalls, allowing them to mitigate the threat the product poses to public health. Within 2 years the fake test strips were fully recalled in the United States, but between 2009 and 2011 customers and investigators still found them in other countries, including Egypt, India, and Pakistan (Loftus, 2011).

As the prevalence of diabetes increases rapidly in the developing world, new, loosely regulated markets attract potential counterfeiters. India is home to more than 50 million diabetics, more than any other country, and the number is expected to increase dramatically over the coming years (World Diabetes Foundation, 2013). In 2007, not long after the first bad test strips appeared in the United States, there were approximately 40.9 million diabetics in India; by the time they reached the country's growing diabetic population the number had risen by more than 10 million (Mohan et al., 2007). As the chronic disease burden increases in developing countries, falsified and substandard versions of the expensive products used to treat them pose new risks.

the proper medical treatment of which is often neglected (Gaziano, 2007; Yusuf et al., 2011).

Maintenance medication for cardiovascular disease is a vulnerable target for fraud, but the need for these drugs is still unmet in much of the world (Gaziano, 2007). In developing countries, there has been a greater emphasis on controlling infectious disease, especially the infectious diseases of childhood. Considerable research indicates that the anti-infective drugs used to do this are often compromised in poor countries.

Medications for Infectious Diseases

Since 1999 the WHO has known that antibiotics are commonly falsified or made improperly (Wondemagegnehu, 1999). In the 1990s antibiotics accounted for over 45 percent of the 771 cases of falsified and substandard medicines brought to the WHO's attention (Wondemagegnehu, 1999). A more recent survey in Egypt, Jordan, Lebanon, and Saudi Arabia found more than half of antibiotics sampled to be substandard (Kyriacos et al., 2008). A similar survey in Burma uncovered substandard drugs in 16 percent of amoxicillin and 13 percent of ampicillin samples (Wondemagegnehu, 1999). More recently, a survey of amoxicillin in the capital of Papua New Guinea found all samples outside of pharmacopeial specifications; 14 percent had undetectable levels of active ingredient (Nair et al., 2011). Chapter 3 describes the depth of the problem of fake antibiotics in more detail.

In most low- and middle-income countries β-lactam antibiotics, an inexpensive and widely available class of drugs that includes penicillin and amoxicillin, are the first-line treatment for dozens of bacterial infections, including scarlet fever, pneumonia, and respiratory and urinary tract infections (Byarugaba, 2004). Pneumonia, for example, is the leading cause of death in children under 5 and accounts for 18 percent of all child deaths in the world (Unicef and WHO, 2006; WHO, 2011b). The pathogen *Streptococcus pneumoniae* causes most of the world's pneumonia. Alone it accounts for as much as 12 percent of all child deaths worldwide (O'Brien et al., 2009). Unicef's recommended strategy for preventing pneumonia deaths is recognizing sickness in the child, seeking medical care, and treating with antibiotics (Unicef and WHO, 2006). This will remain the best strategy until the pneumococcal conjugate vaccine becomes more widely available. The treatment of pneumonia and other devastating bacterial infections depends on effective antibiotic supply. No research to date has attempted to quantify the proportion of child deaths attributable to falsified and substandard medicines, but Table 2-1 presents the most common causes of child death and links them to verified reports of substandard medicines.

Vaccines are also important in the control of infectious disease. Chapter 5 describes the medicines supply chain in developing countries; in

general, the vaccine supply chain is simpler, if only because Unicef manages the parts of the chain between the manufacturer and the national port of entry (Kauffmann et al., 2011). Cases of falsified and substandard vaccines are rare, but Box 2-2 describes some.

If antibiotics are some of the oldest and most widely used medicines in the world, antiretrovirals are their opposites: new medicines, prescribed in complicated regimes, to a relatively small segment of the population. An exhaustive WHO survey of antiretroviral drug quality in seven sub-Saharan African countries and a variety of treatment centers found reliable good quality in HIV medications (WHO, 2007). Only 1.8 percent of the drugs tested failed to meet quality specifications, and even those were "[not] serious failures, i.e., no critical deficiencies which would pose a serious risk to patients" (WHO, 2007, p. 19).

BOX 2-2
Deaths from Substandard and Falsified Vaccines

Vaccines are complicated to make, and there are relatively few manufacturers supplying the world market. Vaccines are generally procured in bulk by governments or UN agencies in a supply chain with few intermediaries. Though cases are rare, substandard vaccines can permeate this supply chain. In 1995, during a meningitis epidemic, about 60,000 Nigeriens were injected with water disguised as meningitis vaccine (Cockburn, 2005). The substandard vaccine caused about 2,500 to 3,000 excess deaths (BASCAP, 1996).

More recently, in China, substandard hepatitis B and rabies vaccines killed or sickened about 100 babies (Jia and Carey, 2011). Precise information regarding the event is scarce due to the Chinese government's denial of a connection between the vaccines and the incidents as well as its control over the Chinese media. According to the Associated Press, the original article in the *China Economic Times* that exposed the scandal stated that four children who died never had a precise diagnosis, but suffered from fevers and convulsions before their deaths; others who became ill were later diagnosed with encephalitis, among other conditions, and some suffered permanent damage (Associated Press, 2010a). About 200,000 doses of substandard rabies vaccine circulated in Jiangsu province in 2010 before a manufacturer recall (Associated Press, 2010b). These vaccines, like the falsified meningitis vaccine used in Niger, convey no immunity to the patient. When herd immunity is an important result of vaccination, there is no such benefit to society. Assuming the patients survive injection with nonsterile, unidentified liquids, they are still at risk for death from the disease they were not inoculated against.

Some more recent reports suggest that falsified antiretroviral drugs may circulate in African countries. In September 2011, falsified and substandard versions of the triple combination therapy Zidolam-N surfaced in Kenya, many samples molding and crumbling in the packages (Taylor, 2011). A year later, in Tanzania, the regulatory authority uncovered falsified antiretrovirals at a district hospital (Athumani, 2012). These failures put HIV patients at risk for disease progression and favor the selection of resistant virus strains (WHO, 2003). As their viral loads increase, these patients are also more likely to transmit the infection, impeding efforts to control the virus.

Although data suggesting compromised antiretroviral drug quality are mixed, there is substantial evidence, presented in Chapter 3, that antimalarials are often of poor quality. Substandard and falsified malaria drugs are especially common in malaria-endemic parts of Africa and Asia. In 2003, substandard sulfadoxine-pyrimethamine was used to treat a malaria epidemic in northwest Pakistan refugee camps (Leslie et al., 2009). Researchers concluded that, as the strain of *P. falciparum* they identified was 90 percent curable when using standard sulfadoxine-pyrimethamine drugs, the substandard medicines, procured from local manufacturers because of drug shortages, were a causal factor in what initially presented as drug-resistant malaria (Leslie et al., 2009). In this example, the effects of the substandard medicine were promptly mitigated. Health workers diagnosed the parasite with microscopy, monitored drug resistance, and checked drug quality using procedures described in the U.S. Pharmacopeia monograph. Good care during initial infection and treatment with an effective second-line drug prevented any deaths, and the onset of cooler weather stopped transmission (Leslie et al., 2009). The prognosis for most people treated with poor-quality antimalarial drugs is worse. Not only will their malaria be untreated, but inadequate treatment favors the selection of resistant parasites, which threaten their entire communities.

Treatment Failure

Individual patients have much to lose from substandard and falsified medicines. These products also encourage drug resistance and thereby threaten population health today and for future generations. This is a particular concern with substandard products where the dose of active ingredient is low and variable and with falsified products diluted by criminals in an effort to pass screening assays. Drug resistance is common in pathogens with short life cycles: viruses, bacteria, and protozoa. Poor-quality antimicrobial medications, taken frequently and, in poor countries, generally taken without professional supervision, contribute to drug resistance.

Antimicrobial Resistance

Antibiotics should be used only when indicated, in the appropriate dose, and for the correct length of time. Ensuring the proper treatment with the right combination of drugs is the underlying principle of Directly Observed Treatment–Short Course (DOTS), the internationally accepted method of tuberculosis surveillance and treatment (WHO SEARO, 2006). DOTS also depends on a safe and reliable drug supply. Poor-quality drugs have been cited as a causal factor for the rise of multidrug-resistant tuberculosis (Kelland, 2012). Over time, the bacteria causing tuberculosis have become increasingly drug resistant. Multidrug-resistant tuberculosis precedes extensively drug-resistant tuberculosis, and finally, sometimes, totally drug-resistant tuberculosis (Udwadia, 2012). Extensively drug-resistant strains of tuberculosis account for about 6 percent of incident infections worldwide, but much more in China, India, and the former Soviet Union (Jain and Mondal, 2008). Figure 2-1 shows the increasing incidence of multidrug-resistant tuberculosis around the world.

Drug-resistant bacteria often surface in hospitals, causing infections that are difficult to treat and are an important killer of adults in low- and middle-income countries (Okeke et al., 2005b; WHO, 2012a). It is difficult to estimate the burden of antimicrobial resistance in low- and middle-income countries, in part because of the dearth of data, especially from francophone Africa, the Asian Pacific, and the former Soviet Union (Okeke et al., 2005a). The data that do exist are grim. Multidrug-resistant staphylococcus, an emerging problem in India and sub-Saharan Africa (Parasa et al., 2010; Vincent et al., 2009), accounts for more than half of all nosocomial infections in parts of Latin America (Guzmán-Blanco et al., 2009). (See Figure 2-2.)

In a qualitative study in Orissa, India, doctors, veterinarians, and pharmacists cited poor-quality antibiotics as a cause of drug resistance, but mentioned it only in passing, focusing more on patient and provider behaviors (Sahoo et al., 2010). This is consistent with most public health literature, which gives great deal of attention to the overuse of antibiotics as contributing to the rise of antimicrobial resistance in general (Byarugaba, 2010; Okeke et al., 2005b) and drug-resistant pneumonia in particular (Unicef and WHO, 2006). Comparatively little work, however, discusses the role of drug quality in encouraging bacterial resistance. Antibiotics that contain low doses of active ingredient cause low circulating levels of the drug in the patient. This contributes to treatment failure and selectively favors the growth of drug-resistant organisms (Okeke et al., 2005b). Resistance is most common among the oldest and least expensive families of antibiotics (Okeke et al., 2005b).

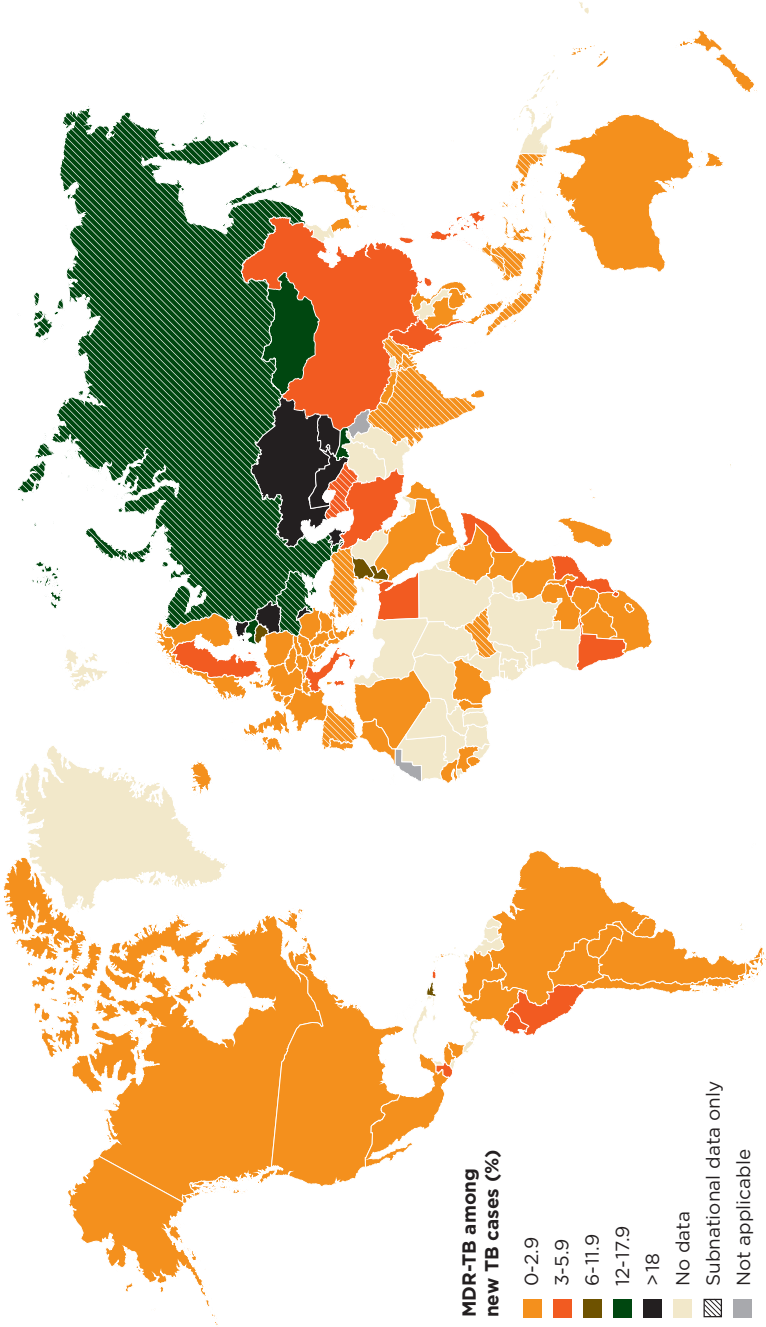


FIGURE 2-1 Increasing incidence of multidrug-resistant tuberculosis (MDR-TB).
SOURCE: WHO, 2011b.

According to a recent Tufts University estimate, it costs more than $1.3 billion to bring a new drug to market (Kaitin, 2010). Antibiotics in particular offer pharmaceutical companies a low return on investment; patients take them for only a week or two, in contrast to lifetime regimes of maintenance drugs. There would be even less monetary incentive to develop antibiotic for only the poorest parts of the world. Preserving antibiotics is imperative and depends on maintaining drug quality as much as on encouraging rational use.

Antimalarial Resistance

Through a conceptually similar mechanism, selectively allowing the growth of drug-resistant parasites by exposing them to subtherapeutic doses of medicines, falsified and substandard drugs favor survival and spread of resistance to antimalarial medicines. Drug-resistant parasites of particular concern are the malaria parasites *Plasmodium falciparum* and *Plasmodium vivax*.

Artemisinin combination treatments are effective in treating falciparum malaria (WHO, 2011d). They have been the recommended first-line treatment for falciparum malaria everywhere in the world since 2001 (WWARN, 2012d). In areas where these drugs are available and appropriately used, malaria deaths have dropped dramatically (WHO, 2011d).

Drug resistance could undo the success that artemisinin therapies have won, however (see Box 2-3). A recent review estimates that about 35 percent of the antimalarial medicines in Southeast Asia are substandard, and 36 percent can be classified as falsified (Nayyar et al., 2012). The same researchers found similar patterns in sub-Saharan Africa, where about 35 percent of antimalarials are substandard and 20 percent are falsified (Nayyar et al., 2012). In both regions, underdosing the active ingredients is far more common than overdosing (Nayyar et al., 2012). Already, 8 of the 12 major antimalarial drugs used in the world have been falsified, including products labeled as of mefloquine, but containing sulphadoxine-pyrimethamine and no mefloquine, and a product labeled as artesunate, but containing 6 percent chloroquine and no artesunate (Newton et al., 2006). Poor-quality medicines supply a subtherapeutic dose that selectively encourages the emergence of partially resistant pathogens (Talisuna et al., 2012).

Underdosing with antimalarials causes low concentrations of active drugs in patients and selective pressure to breed resistant parasites (Dondorp et al., 2011; Sengaloundeth et al., 2009; White et al., 2009). In Thailand investigators have observed a progressive lengthening of the time it takes for patients to clear malaria parasites from their bloodstream during treatment, suggesting that the parasites are becoming more resistant to artemisinin (Phyo et al., 2012). Resistance is heritable from one generation

FIGURE 2-2 Percentage of nosocomial *Staphylococcus aureus* isolates with resistance to meticillin in studies in Latin American countries.

NOTE: Countries in orange are those with >50 percent of nosocomial *S. aureus* isolates were found to be meticillin-resistant in at least one report.

SOURCE: Guzmán-Blanco et al., 2009. Reprinted with permission from Elsevier.

of parasite to the next; the relatively resistant parasites persist and are transmitted (Anderson et al., 2010). So far, artemisinin resistance has been documented only in Southeast Asia, but its persistence and spread could threaten global malaria control programs. No other antimalarial drugs are available as alternatives. If the current first-line therapy is lost because of resistance, malaria deaths will again increase.

Other Antiparasitic Resistance

Confirming drug resistance in parasites is more complicated than the same assessment in bacteria (Cabaret, 2010). There is good evidence, however, that underdosing with anthelmintic medication has favored survival of resistant worms, and substandard medicines are a noted contributor to anthelmintic resistance in both humans and animals (Geerts and Gryseels, 2001).

Drug resistance threatens efforts to contain other neglected tropical diseases. Visceral leishmaniasis, also called kala azar, is a parasitic disease that affects a half a million people per year, mostly in South Asia, and also in Brazil and Sudan (Sundar, 2001). Untreated kala azar is fatal, but pentavalent antimonial drugs have been a reliable therapy since the 1930s. Pentavalent antimonials are still a first-line treatment today, but drug resistance has diminished the potency of these drugs (Sundar, 2001). A high-osmolarity batch of pentavalent antimonials induced congestive heart failure, killing three kala azar patients and sickening many more at Benares Hindu University hospital in the late 1990s (Sundar et al., 1998). Since then, substandard medicines have been a suspected factor in the increasing resistance of the kala azar parasites to traditional treatment (Sundar, 2001). Newer therapies, such as miltefosine, hold promise for containing the disease, but this promise will not be realized unless the drugs are of reliable quality. As recently as 2012, a convenience sample of miltefosine in Bangladesh found the drugs to be uniformly devoid of any active ingredient (Dorlo et al., 2012).

ECONOMIC AND SOCIAL CONSEQUENCES

Substandard and falsified medicines effect health directly and pose a danger to individual patients and to public health. They also have economic

Key Findings

- Treatment with substandard and falsified drugs wastes time and money, raising drug costs to patients and the health system.
- Drug resistance reduces the effective life of a drug, and society must bear the cost of new drug development.
- A compromised drug supply causes consumers to lose confidence in medicine, health care providers, and national regulatory agencies.
- The sale of falsified medicines funds criminal activities and conveys power to corrupt officials.

BOX 2-3
The WorldWide Antimalarial Resistance Network

Despite the success of malarial control programs starting in 2004, malaria is still a major cause of death, especially in Africa (Murray et al., 2012). WHO estimates that about 655,000 people die from malaria every year, though a recent systematic analysis suggested the true annual mortality is closer to 1.24 million (Murray et al., 2012). Inexpensive oral drugs—chloroquine and sulfadoxine-pyrimethamine—were once common treatment for malaria, but resistance to these treatments is widespread (WHO, 2012c). Since 2001, the WHO has recommended treating malaria with artemisinin combination therapies (WWARN, 2012c). The use of artemisinin combination drugs as first-line therapy is essential to malaria control. As of 2006, however, there is evidence of artemisinin resistance in Southeast Asia (WWARN, 2012c).

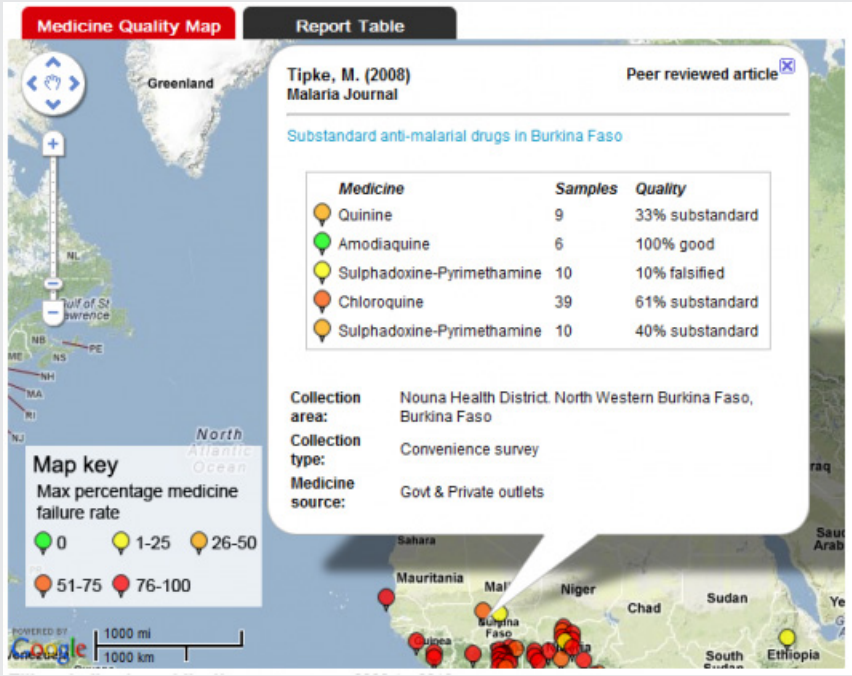
The WorldWide Antimalarial Resistance Network (WWARN) is a multidisciplinary, worldwide network of malaria experts run by Oxford University. WWARN is divided into six scientific working groups, including a group that works to encourage research on antimalarial drug quality. To this end, they give step-by-step guidance on field surveys, develop standard reporting and data collection forms, and review chemical assays and packaging analysis protocols (WWARN, 2012a). They also manage online forums to discuss drug quality in English and French (WWARN, 2012a).

WWARN also created a interactive internet database that shows the spread of poor-quality antimalarials over time and space (Tabernero and Newton, 2012). The system maps scientific and lay reports of antimalarial medicine quality. Users can view hotspots as points on a map or in table; they can filter information by medicine, report type, data collection method, medicine source, and date. This tool makes information about antimalarial quality more readily available to regulators and malaria control teams, which in turn improves action against the problem. Future versions of the surveyor will include brand and manufacturer information, as well as graphs of emerging trends and photos of different medicines and packaging (WWARN, 2012b).

and social consequences, including the direct costs of additional treatment and indirect social costs of lost confidence in the health system and the government.

Costs to the Health System

First, the use of falsified and substandard medicines costs the health care system. Providers do not usually suspect that the drugs they prescribe are of poor quality and will respond to a poor therapeutic response by



A WWARN online drug quality map.

ordering more tests or by repeating the course of treatment. In poor countries, where medicines rank second only to food as a household expense (Cameron et al., 2008), an increase in the family medicines bill can be a palpable hardship. When government or donors supply medicines, they shoulder the added costs of falsified and substandard drugs.

Chapter 4 describes the pressure on procurement agencies to fill drug orders for the lowest prices, a false frugality that can cause the wasting of an entire medicines budget on drugs with insufficient active ingredients. The costs only grow when expensive drugs are targeted or when they are

Pharmacy in Cambodia.
SOURCE: Hen Sophal in Pharmacide Arts, an exhibit of Southeast Asian artists.

sold in rich countries. It is not yet clear how much patients and insurance companies paid for falsified Avastin during the 2012 crisis, but the *Wall Street Journal* found that the fake product sold for almost $2,000 per vial (Weaver and Whalen, 2012).

Drug resistance will increase costs to the health system, and not only because of increased clinical attention. Drug resistance reduces the effective life of a drug. Already the cheapest, oldest classes of anti-infective drugs are becoming useless. Society must bear the expense of new drug development, an ever-increasing cost (see Figure 2-3), because resistant pathogens require treatment with more complex drugs. A 2010 estimate put the cost of developing a single drug at $1.3 billion (Kaitin, 2010), and a 2003 study showed that the cost of drug development grew 7.4 percent faster than inflation (DiMasi et al., 2003).

Aside from the direct financial costs of treatment, there are opportunity costs incurred to patients who miss work for additional doctors' visits or become too sick to work. Chapter 3 will explain that the burden of falsified and substandard medicines is borne mostly by the poor in South and Southeast Asia and sub-Saharan Africa. Transport costs and opportunity costs are a known obstacle to health care for these patients (Whitty et al., 2008). Customers at gray pharmaceutical markets, including flea markets,

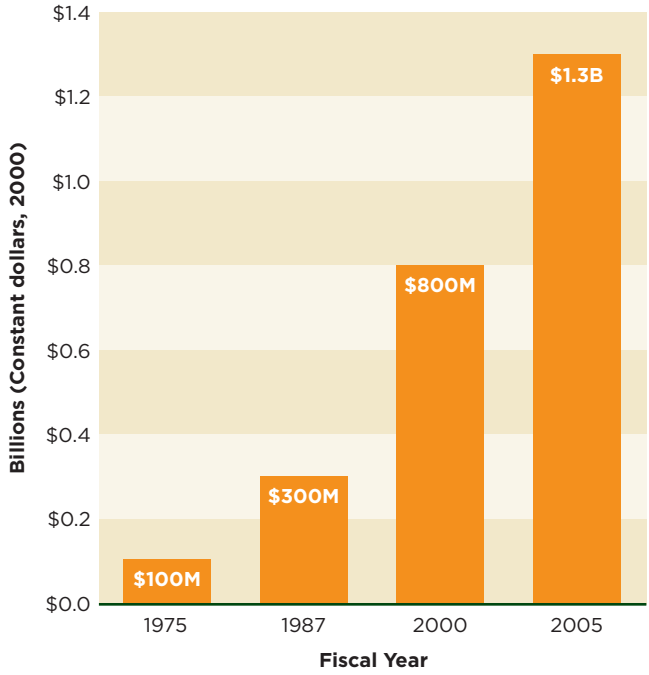


FIGURE 2–3 The increasing costs of drug development.
SOURCE: PhRMA, 2012.

unlicensed medicine shops, and bazaars, are often there because they cannot afford to miss work for a formal consultation (Whitty et al., 2008). For example, participants at the São Paulo site visit for this study explained that although medicines are free through the public health system in Brazil, miners and other daily-wage workers circumvent this system. They continue working and self-treat with medicines of dubious quality from the gray market. In Brazil, as in many parts of the world, falsified and substandard medicines extract the highest costs from those who can afford the least.

Scientists and policy makers in developing countries are aware of the toll falsified and substandard drugs take on their health systems. A 2009 WHO expert working group rated fake medicines as a top priority for research in developing countries (Bates et al., 2009).

Patients may begin to distrust modern pharmacies after experiences with falsified and substandard drugs. In Ugandan villages, the proportion of positive responses to the question "Do you expect that the antimalarial medicines sold by the nearest drug shop are fake?" correlates roughly

with the actual percentage of poor-quality drugs (Björkman-Nyqvist et al., 2012).

As well as having accurate doubts about individual pharmacies, consumers in places where fake drugs circulate have reason to lose faith in the public health system. A recent systematic review suggests that patients across a range of developing countries already have poor perceptions of the health system, especially the technical competence and clinical skills of the staff and the availability of medicines (Berendes et al., 2011). Poor-quality medicines stand to damage the perception of the health system even more. Qualitative research in China suggests that patients view the loosely regulated private health care system poorly, seeing it as rife with "fake doctors" and "fake drugs" (Lim et al., 2004, p. 227).

During a site visit to Brazil, the IOM delegation heard that, although the Brazilian drugs regulatory authority is strong, the public still doubts the quality of many medicines. Participants consistently attributed this poor confidence to unplanned pregnancies following a 1998 lapse in the quality of oral contraceptives (Associated Press, 1998; Goering, 1998). Anvisa, the Brazilian drugs regulatory authority, was created in response to this and other medicine quality problems (Csillag, 1998). Rumors about contraceptive quality linger in Brazil, a kind of urban folklore. They are evidence, however, that fake medicine can do long-term damage to the reputation of the health system.

Social and Developmental Costs

In a larger sense, trade in falsified and substandard medicines undermines not just the health system but all public institutions. Corruption in the health system can cause patients to assume the drug supply is substandard (BBC, 2012). Falsified medicines are often the business of criminal cartels, including the Camorra crime group in Naples, the Russian mafia, and Latin American drug cartels, and terrorist organizations, such as Al-Qaeda and Hezbollah (Findlay, 2011). These organizations run profitable and untaxed businesses. Organized crime flourishes under authoritarian governments and weak rule of law, both common in developing countries (UNODC, 2009). Criminals grow wealthy under either system, eventually wealthy enough that tacit (or active) collaboration becomes necessary for private citizens and politicians to survive (UNODC, 2009). When criminals control politicians, governments cannot be trusted. Donors are then obliged to withhold development aid, as several countries have done in response to corruption in the Zambian health ministry (BBC, 2010; WHO, 2009).

The sale in falsified medicines funds other criminal activities, buys weapons and ammunition, and conveys power and influence to corrupt officials (Findlay, 2011; UNODC, 2009). The United Nations Office on

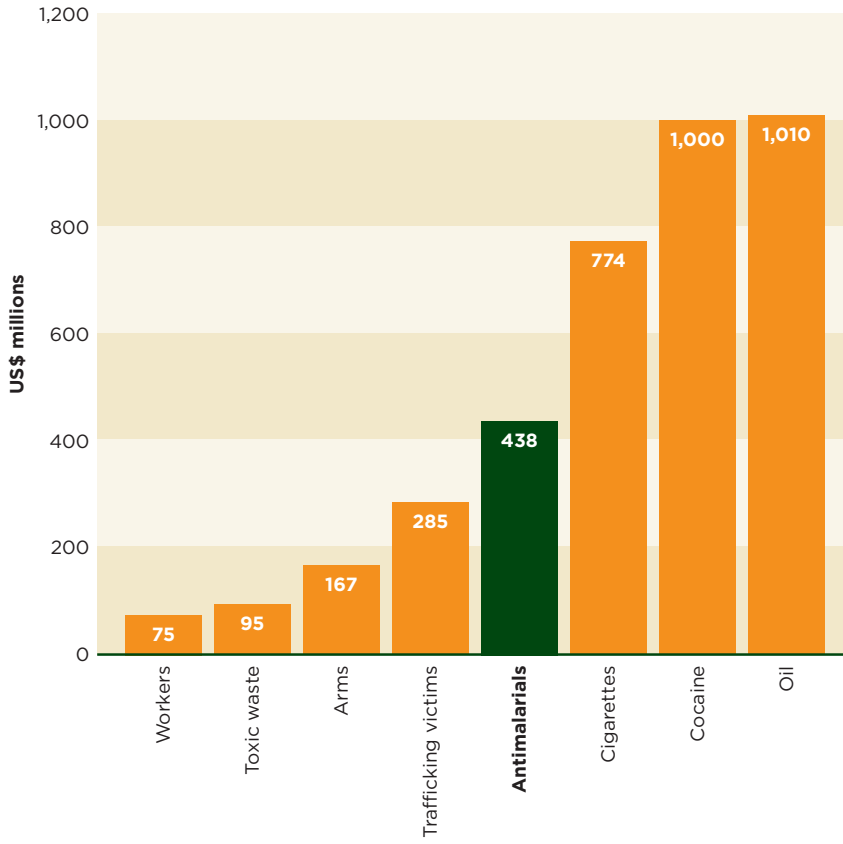


FIGURE 2–4 Comparative values of trafficking flows in West Africa.
SOURCE: UNODC, 2009.

Development and Crime (UNODC) reckons that in West Africa the sale in falsified medicines may be worth as much as the billion-dollar oil and cocaine trafficking industries; their estimate of the worth of trafficked antimalarials alone is more than $400 million (see Figure 2-4).

Chapter 4 describes why medicines fraud is sometimes called the perfect crime. Fake medicines generate income for criminals, and only the weakest evidence, if any, ties them to their crime. Acute cases of medicine poisoning can elicit public outcry, but more often bad drugs go unnoticed, blending in with lawful business. Victims of falsified and substandard drugs usually do not even know they are victims and are therefore deprived of their right to redress. The UNODC described the traffic in fake drugs as both as cause and an effect of political instability, explaining, "Living in a society where

such widespread and serious fraud can occur undermines confidence in government, but the effects are so diffuse and uncertain that they are unlikely to generate an organized political response" (UNODC, 2009, p. 6). In many parts of the world, falsified and substandard medicines further erode the already weak political infrastructure that allows them to circulate, part of a vicious cycle of poverty and crime.

TABLE 2–1 Medicines Used to Treat the Most Common Causes of Child Death Are Compromised in Developing Countries

	Common Pathogen	Essential Medicine	Known Falsified or Substandard or Both?
Pneumonia	*Streptococcus pneumoniae*	Amoxicillin	Yes[a,b,c]
		Amoxicillin + clavulanic acid	Yes[a,d]
		Ampicillin	Yes[a,b,e]
		Trimethoprim-sulfamethoxazole	Yes[a]
	Pneumocystis carinii	Trimethoprim-sulfamethoxazole	
	Mycoplasma pneumoniae	Erythromycin	Yes[a,f,g]
	Haemophilus Influenzae type b	Ampicillin	Yes[a,b,e]
Diarrheal Diseases	*Rotavirus*	Oral rehydration solution (ORS); zinc sulfate	
	Campylobacter jejuni	Oral rehydration solution (ORS); zinc sulfate	
		Erythromycin	Yes[a,f,g]
	Escherichia coli	Oral rehydration solution (ORS); zinc sulfate	
	Vibrio cholerae	Oral rehydration solution (ORS); zinc sulfate	
		Erythromycin	Yes[a,f,g]
		Doxycycline	Yes[a,h]
	Shigella	Oral rehydration solution (ORS); zinc sulfate	
		Ampicillin	Yes[a,b,e]
		Trimethoprim-sulfamethoxazole	Yes[a]
		Ceftriaxone	Yes[a]

continued

TABLE 2-1 *Continued*

	Common Pathogen	Essential Medicine	Known Falsified or Substandard or Both?
Malaria	*Plasmodium vivax/ovale/falciparum/malariae*	Amodiaquine	Yes[i,j]
		Artemether	Yes[i,k,l]
		Artesunate	Yes[k,l,m]
	Plasmodium vivax/ovale/falciparum/malariae	Doxycycline	Yes[a,h]
		Mefloquine	Yes[k,n]
		Sulfadoxine/pyrimethamine	Yes[l,j,o]
		Quinine	Yes[j,k,o]
		Artesunate + amodiaquine	Yes[l]
		Artemether + lumefantrine	Yes[l]
	Plasmodium vivax	Chloroquine	Yes[f,k,p]
		Primaquine	
	Plasmodium ovale	Primaquine	Yes[q,r]

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3

The Magnitude of the Problem

It is difficult to accurately measure the burden of falsified and substandard drugs. As Chapter 2 mentions, some of the understanding of the problem comes from alerts in gray literature, including investigative journalism and industry and association reporting. Although these sources provide some insight, they do not provide an accurate estimate of the true magnitude of the problem. National regulatory authorities and drug companies keep records on fraudulent medicines; a broader understanding of the problem comes from peer-reviewed literature. There are few epidemiologically rigorous, peer-reviewed studies on the prevalence of falsified and substandard drugs.

This chapter presents the results of a cross section of government and industry data and peer-reviewed and gray literature about the global burden of falsified and substandard drugs. It does not summarize every study, but rather gives an overview of important trends.

INDUSTRY AND GOVERNMENT DATA

Both industry and governments have data on medicines quality, but little of this information is public. There was a time when this was a conscious secrecy, an effort to avoid discrediting the public health system and drug companies, expressed in the Royal Pharmaceutical Society's 1989 statement "no great publicity [about fake drugs] should be sought because it could damage public confidence in medicines" (Cockburn et al., 2005; More UK debate on counterfeits, 1989). The society has since changed its policy, but the essence of the problem remains. Governments may wish to

Key Findings and Conclusions

- Public data on the magnitude of the problem of substandard and falsified medicines are limited.
- The illegal trade and manufacture of medicines are a global problem, disproportionately affecting low- and middle-income countries.
- Countries with weak regulatory oversight and law enforcement attract illegitimate manufacturers, while countries with strict law enforcement repel them.
- Government and intergovernmental agencies, such as the U.S. Food and Drug Administration and Interpol, have taken action against substandard and falsified medicines.

control rumors that can be seen as damaging to their institutions. Similarly, drug companies, both innovator and generic, may withhold information about falsified and substandard medicines on the grounds that such stories discourage patient confidence in their products (Cockburn et al., 2005).

There is a difference between secrecy and appropriate discretion with evidence for pending criminal prosecutions. The committee recognizes that undercover intelligence informs law enforcement agencies' actions against criminals. Prematurely releasing confidential information about pharmaceutical crime can compromise an investigation. Too often, however, governments and industry withhold information years after incidents pass (Cockburn et al., 2005). Regulators should be able to access this data so that they can communicate it to the public as appropriate, as it informs consumer safety and can trigger epidemiological research on drug quality.

There is also value in sharing information on falsified and substandard medicines internationally. The modern pharmaceutical supply chain is complex. Drug manufacturers source chemicals from around the world, and different factories process ingredients into a final formulation that is packaged, repacked, and sold in many different countries. The chances that a drug quality problem in one country affects that country alone decrease when products travel along global supply chains. The interconnectedness of the drug supply chain makes it imperative that countries share information on falsified and substandard drugs.

The Pharmaceutical Security Institute Incident Reporting System

The Pharmaceutical Security Institute (PSI) is a nonprofit organization composed of the security departments of 25 major pharmaceutical compa-

nies (PSI-Inc., 2012b). These companies share information on illegal pharmaceutical manufacture and trade. Because criminals who make and traffic illegal drugs target a wide range of companies' products, cooperation and data sharing among companies adds depth to their collective understanding of the problem.

The institute maintains a secure database to which members report cases of fraudulent manufacture and mislabeling of drugs, as well as cases of fraudulent packaging. The database is organized into incidents, "discrete event[s] triggered by the discovery of counterfeit, illegally diverted, or stolen pharmaceuticals" (PSI-Inc., 2012a). A unique tracking number links every incident to a distinct date, time, place, and product. Incidents can vary in size; sometimes, small amounts of a single product are affected, other times large quantities of many products (PSI-Inc., 2012a). Some incidents last for years while others are resolved in 1 year. Incidents that lasted several years are dated with the year in which the incident started (PSI-Inc., 2012a).

An analysis of the institute's data gives an understanding of where law enforcement and regulators are active against the illegal trade and manufacture of drugs. Some countries with serious problems never appear in incident reports because there is little political will for action. For the same reason, some countries with transparent and accountable governments consistently appear in the ranking of numbers of seizures by countries (PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012). Table 3-1 presents the 2011 rankings of the top 12 countries where PSI members detected[1] or where police, customs, or drug regulators seized falsified products.

The illegal manufacture and trade of medicines is transnational. Table 3-1 shows only those countries where government or industry staff *found* a bad product; many more countries stand to be affected by those products. If a shipment of falsified pills comes from China to the United States via India, then the incident report names all three countries. Table 3-2 ranks the 10 countries most often cited in PSI incident reports. The countries listed in Table 3-2 account for 56 percent of illegal manufacture, trade, or sale and 47 percent of diversion cases in the PSI 2011 database (personal communication, Thomas Kubic, PSI-Inc., December 26, 2012).

In addition to naming affected countries, every incident report in the PSI database mentions the drugs targeted. Every therapeutic class of drugs is represented in these reports, though genitourinary, anti-infective, and cardiovascular drugs are the most often implicated (PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012). Criminal interest in cardiovascular disease drugs is a new trend; only in 2011 did that class

[1] Detection means confirming though chemical or package analysis that the product is not what it purports to be.

TABLE 3–1 Ranking of Seizures or Detections by Country, 2011

	Country	Incidents
1	**China**	279
2	**United States**	141
3	**Japan**	79
4	**Germany**	62
5	**Pakistan**	61
5	**Peru**	61
7	**Colombia**	59
8	**United Kingdom**	56
9	**South Korea**	47
10	**Brazil**	45
10	**Russia**	45
12	**Taiwan**	44

SOURCE: PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012.

of medicines move into the top three most commonly targeted (PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012). This is consistent with other industry reports that drugs sold and restocked frequently are most often targeted (Mukherjee, 2012).

PSI member companies identified 1,623 counterfeiting incidents in 2011. In about half of these incidents (n = 810) companies were able to do product and packaging analysis. Investigators found that most samples were fraudulent in both product and packaging (see Figure 3-1). A false product in legitimate packaging was the second most common result; Chapter 5 discusses this problem in more detail.

Analysis of PSI data supports two main conclusions. First, falsified and substandard drugs are a global problem that affected at least 124 countries in 2011 (PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012). Twelve more countries were affected in 2011 than in 2010; African countries accounted for most of this increase (PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012). The data do not suggest anything about the relative burden of the problem in different countries, however. Indeed, countries with lax enforcement attract illegal manufacturers, and countries with vigorous law enforcement repel them.

TABLE 3–2 Ten Countries Most Named in PSI Incident Reports, 2011

	Country	Counterfeit[a]	Diversion	Theft[b]	Total Incidents
1	**China**	504	8	0	512
2	**United States**	145	62	8	215
3	**India**	95	23	0	118
4	**Brazil**	47	47	3	97
5	**Colombia**	62	32	0	94
6	**Japan**	81	0	0	81
7	**United Kingdom**	61	17	2	80
8	**Germany**	64	10	0	74
9	**Uzbekistan**	35	37	0	72
10	**Pakistan**	64	7	0	71

NOTE: PSI = Pharmaceutical Security Institute; WHO = World Health Organization.

[a]PSI uses the term *counterfeit* broadly, in accordance with the WHO definition: "one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients, wrong ingredients, without active ingredients, with insufficient quantity of active ingredient or with fake packaging" (WHO, 1992, 2009). See page 23.

[b]Incident reports include thefts worth roughly $100,000 or more.

SOURCE: PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012.

Second, PSI data suggest that the problem is borne disproportionately by low- and middle-income countries. Figure 3-2 shows *Business Monitor International*'s (BMI's) global distribution of pharmaceutical sales; Figure 3-3 shows geographic distribution of PSI's 2011 incidents. Admittedly, the Asia category in both figures includes rich countries such as Australia and Japan (personal communication, Mariam Kahn, *Business Monitor International*, October 23, 2012). The higher cost of living, higher incomes, and greater access to medicines in North America and Europe also account for these regions' large share of pharmaceutical sales. Nevertheless, North America and Europe make up almost two-thirds of the world's combined pharmaceutical sales but account for only a quarter of global trade in illegal medicines. PSI data come from the investigations of multinational, innovator pharmaceutical companies. One would expect a bias in these data to developed country markets, where PSI member companies earn most of their profits. However, even PSI data suggest a serious problem with falsified medicines in low- and middle-income countries.

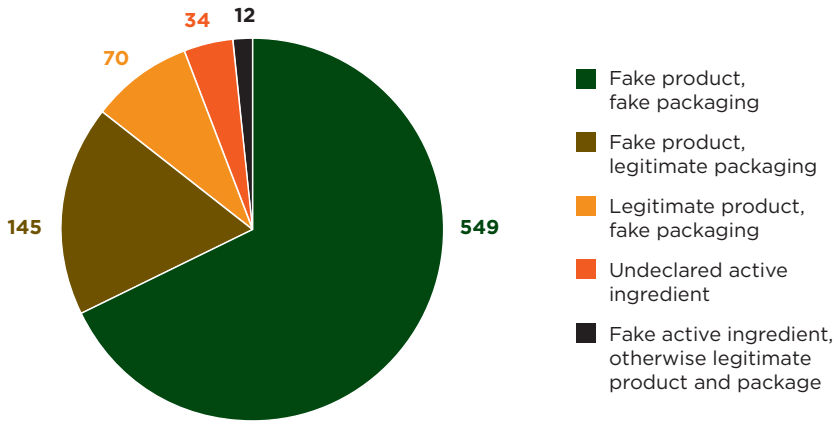

FIGURE 3–1 Results of packaging and product analysis, 2011.
SOURCE: PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012.

Government and Intergovernmental Investigations

National regulatory agencies have the main responsibility for monitoring drug safety (WHO, 2012a). This includes routine postmarket surveillance and enforcement of regulations. Much of their information about falsified and substandard drugs is confidential, but their publications give a sense of the types of violations regulators find.

The FDA Office of Criminal Investigations

The FDA Office of Criminal Investigations takes action against criminal violations of the Food, Drug, and Cosmetic Act, such as illegal drug manufacture, manufacture and sale of unapproved drugs, illegal importation, drug adulteration, and promotion of off-label uses for approved products (FDA, 2009a,b). In May 2012, the office briefed the committee on their work from 2003 to 2008. This presentation and a 2011 review of the agency's drug criminal cases give some understanding of common problems with the drug supply in the United States (Devine and Jung, 2012; FDA, 2011). These data illustrate certain problems with the drug supply chain but are not a "scientific representation of current . . . trends or a comprehensive review of problems" (FDA, 2011, p. 4).

The FDA has investigated increasingly more drug quality cases since

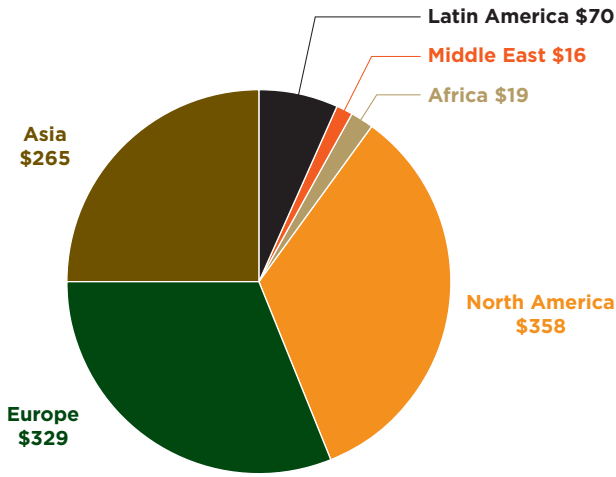

FIGURE 3–2 Geographic distribution of pharmaceutical sales in $U.S. billions, 2011 data.
SOURCE: BMI, 2012.

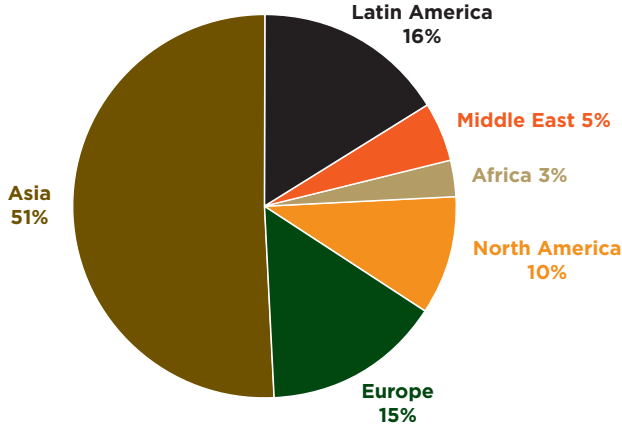

FIGURE 3–3 Geographic distribution of Pharmaceutical Security Institute incident reports, affected countries, 2011 data.
SOURCE: Personal communication, Thomas Kubic, PSI-Inc., October 18, 2012.

1997[2] (Devine and Jung, 2012). Solid oral dosage forms (pills and tablets) are the most commonly investigated product types (FDA, 2011). Zyprexa, Viagra, Lipitor, Zoloft, and Risperdal are the top 5 brand-name products implicated in the 10 highest-volume cases (FDA, 2011). Problems with individual criminals are more common than problems with negligent businesses; the FDA's 2003-2008 review found that 86 percent of criminal investigations were of individual suspects, and 14 percent were of companies (FDA, 2011).

International Police Investigations

Interpol is an international organization that facilitates police cooperation around the world (Interpol, 2012c). The organization gives training and investigative support to police in 190 member countries (Interpol, 2012c). Pharmaceutical crime, which the organization defines as "counterfeiting and falsification of medical products, their packaging and associated documentation, as well as the theft, fraud, illicit diversion, smuggling, trafficking, [and] the illegal trade of medical products and the money laundering associated with it" has been an Interpol work area since 2005 (Interpol, 2012d; Plançon, 2012). Interpol organizes their work into four operations: Operation Pangea (against illegal online pharmacies), Operation Mamba (in East Africa), Operation Storm (in Southeast Asia), and Operation Cobra (in West Africa) (Interpol, 2012a). Tables 3-3 and 3-4 give an overview of these operations.

As Table 3-3 and 3-4 indicate, police have seized millions of pounds of suspect drugs in Interpol operations. Some police forces sample and report the quality of the products found in these seizures. The police are not obliged to undertake such investigations or report their results to Interpol; in many countries, testing even a small sample of confiscated product would overwhelm the national drug quality laboratory. Interpol does not publish information on the testing and sampling of seized products.

Interpol has raised international awareness about falsified and substandard drugs through their media campaigns and work with police (Interpol, 2011a; Mullard, 2010). Nevertheless, the information presented in Tables 3-3 and 3-4 does not indicate which kinds of drugs are targeted or if the problem is changing over time.

[2] The FDA refers to these as counterfeit drug cases. The agency uses a definition of *counterfeit* that includes both *falsified* and *substandard* as this report defines them. See Table 1-2.

TABLE 3–3 Operation Pangea Against Online Pharmacies, 2008-2012

Operation Name	Number of Countries Participating	Duration	Year	Results
Pangea V	100	1 week	2012	• 3.75 million pills confiscated • Estimated value: $10.5 million • 18,000 websites shut down • 133,000 packages inspected and 6,700 confiscated • 80 suspects under investigation or arrest
Pangea IV	81	1 week	2011	• 2.4 million pills confiscated • Estimated value: $6.3 million • 13,500 websites shut down • 45,500 packages inspected and 8,000 confiscated • 55 suspects under investigation or arrest
Pangea III	44	1 week	2010	• 2 million pills confiscated • Estimated value: $6.77 million • 297 websites shut down • 87 suspects under investigation or arrest
Pangea II	25	5 days	2009	• Identification of 1,200 websites engaged in pharmaceutical crime • 153 websites shut down • 59 suspects investigated
Pangea I	10	1 day	2008	• Commercial websites taken down • Postal deposits monitored and parcels examined, packages containing suspected counterfeit medicines intercepted • Thousands of medicines withdrawn from circulation

SOURCE: Adapted from Interpol, 2012b.

TABLE 3–4 Operations Storm, Mamba, and Cobra, 2008-2011

Operation Name	Number of Countries Participating	Duration	Year	Results
Storm II	8	1 month	2010	• 20 million pills seized • More than 100 illicit drug outlets closed • 33 arrests
Storm I	8	5 months	2008	• 186 raids • Estimated value: $6.65 million • 27 arrests
Mamba III	5	2 months	2010	• 200,000 pills seized • 375 premises targeted • 120 police cases opened, 78 prosecutions, 34 convictions
Mamba II	3	1 month	2009	• Thousands of tablets seized • 270 premises targeted • 83 police cases opened • 4 convictions
Mamba I	2	1 week	2008	• More than 100 different products seized • 262 premises inspected • 82 police cases opened
Cobra	7	1 week	2011	• 5,500 boxes of medicines seized • More than 100 arrests

SOURCE: Adapted from Interpol, 2010a,b, 2011b.

CASE REPORTS AND CONVENIENCE SAMPLES

Scientific literature contains valuable reports of drug contamination; often clinicians uncover fake drugs in the course of their practice. Newspapers, court documents, and other gray literature sources also contain valuable information about drug quality lapses. Convenience surveys and case reports can be useful for identifying a problem in particular product lines or building momentum for further research.

The following brief analysis of convenience surveys and case reports indicates that drug quality lapses happen around the world. In countries with strong regulatory systems, the problems are often confined to gray market purchases of the so-called lifestyle drugs, medicines for erectile dysfunction and cosmetic conditions. In poor countries a wide range of products are compromised, including most essential medicines.

Key Findings and Conclusions

- Case studies and postmortem investigations generate interest in substandard and falsified drugs. These reports can drive epidemiological research.
- Convenience surveys suggest serious problems with antimicrobial drug quality in low- and middle-income countries, and especially with antimalarial quality in sub-Saharan Africa and Southeast Asia.

Case Reports

A great deal of literature on falsified and substandard drugs describes problems that emerge only after patients have been harmed (Ravinetto et al., 2012). These reports do not set out to comment on the regional burden of poor drug quality or trends in compromised products, but they are useful for other reasons. Many of these stories receive significant media attention, encouraging public interest in the problem. Case studies also give understanding of the social and environmental conditions that foster problems with falsified and substandard drugs (Pew, 2012).

Patient case studies are a common type of incidental investigation. For example, the rapid deterioration and death of a Burmese patient with uncomplicated malaria triggered a drug analysis that found the medicines used to treat him were both falsified and substandard (Newton et al., 2006). A postmortem investigation in a previously healthy, 58-year-old Canadian woman found that her death was from acute metal poisoning from a variety of falsified and substandard drugs, many of them antianxiety and antidepressive medications she bought from the internet (Solomon, 2007).

Individual deaths can trigger drug quality investigations; mass causalities are clearly more likely to rouse suspicion. Chapter 2 describes one such incident, when a Panamanian physician reported on a spike in cases of acute renal failure, accompanied by neurological dysfunction, abdominal symptoms, urinary irregularities, anorexia, and fatigue (Rentz et al., 2008). A case-control investigation found diethyelene glycol poisoning to be the cause of the outbreak (Rentz et al., 2008). Later investigations, including a Pulitzer Prize–winning *New York Times* series, implicated falsified ingredients from China in an international poisoning crisis (Bogdanich, 2007; Rentz et al., 2008).

Newspaper reports and other gray literature sources also contain a wealth of information about drug quality problems. Monitoring this literature is a valuable way to follow what drugs are compromised and where. The U.S. Pharmacopeia's *Media Reports on Medicine Quality Focusing on*

USAID-Assisted Countries is a useful gray literature compendium (PQM, 2012). Reports are organized by country and medicine affected. The compendium contains links to government and academic surveys as well. The reports presented in the compendium suggest that a range of drugs are compromised in low- and middle-income countries. Antimicrobial drugs are often mentioned, but oral contraceptives, the anti-influenza drug oseltamivir, antihypertensives, antidepressants, blood thinners, and drugs for erectile dysfunction are also frequently named (PQM, 2012). The last section lists international and global incidents, many tied to the internet (PQM, 2012).

The Pharmaceutical Security Institute also monitors gray literature; their open-source database contains publicly available records of the types of medicines compromised, arrests for pharmaceutical crime, and other details staff can glean from public reports (PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012). Table 3-5 summarizes the organization's 2011 open-source review.

An overview of case studies and gray literature is helpful to understanding falsified and substandard drugs. Gray literature compendiums and peer-reviewed case studies indicate where and in what product lines drug quality problems occur. Such reports raise awareness of the problem and can trigger scientific investigation and convenience sampling. Gray literature reports do not often give details of quality testing of compromised samples, but they generally describe products so grossly and obviously compromised that confirmatory lab testing would be unnecessary.

Convenience Samples

A convenience sample is a no-probability sample chosen for its accessibility to researchers, not from an a priori sampling frame. Research on drug quality often uses convenience samples of pharmacies or dispensaries. Convenience studies are logistically simpler than probability-based studies and can be less expensive (Newton et al., 2009). Although useful for identifying problems, results of these studies cannot accurately estimate the population prevalence of poor-quality drugs. They do, however, suggest signals for further research (Newton et al., 2009). This section presents the results of some key convenience studies and review papers.

Antimicrobial Drugs

Antimicrobial drugs treat bacterial, viral, fungal, and parasitic diseases. There are considerable data to suggest that antimicrobial drug quality, particularly the quality of antibiotics and antimalarials, is a problem in low- and middle-income countries. In 2007 Kelesidis and colleagues conducted a comprehensive literature review on antimicrobial drug quality, reviewing

gray literature sources as well as English-language papers published between 1966 and 2006 (Kelesidis et al., 2007). They found that a lack of methodological detail prevented pooling or interpreting aggregate results (Kelesidis et al., 2007). As Table 3-6 indicates, they found reason for concern with antibiotic quality in low- and middle-income countries, though reports of poor-quality antibiotics surface all over the world, including the United States and Europe (Kelesidis et al., 2007). A year later, a study of 111 amoxicillin samples collected in four Arab countries found that 56 percent failed U.S. Pharmacopeia testing (Kyriacos et al., 2008). It is difficult, however, to draw firm conclusions about substandard drug production from these studies. Antibiotics degrade quickly in warm climates; it is hard to distinguish substandard manufacture from poor storage and handling.

Weaknesses in drug registration may complicate convenience surveys. When researchers test only authorized products, they bias their sample against the unregistered products used by the poorest (Seear et al., 2011). Some convenience samples have compared the quality of approved and unapproved products. Between 2008 and 2012, Bate and colleagues collected samples of 2,652 anti-infective drugs from around the world: 11 African cities, 3 Indian cities, Bangkok, Beijing, Istanbul, Moscow, and São Paulo. They found that less than one-third of products had stringent-regulatory agency approval or WHO prequalification (Bate et al., 2012). While only 1.01 percent of stringent-regulatory-agency–approved products failed quality testing, 6.80 percent of WHO-approved drugs failed, and 13.01 percent of products approved by neither the WHO nor a stringent regulatory agency failed (Bate et al., 2012). The report mentions that the failure rates were higher among samples from Africa than among samples from middle-income nations (Bate et al., 2012). Similarly, a WHO study in found that only 43 percent of essential anti-infective medicines[3] sampled in Vietnam were registered, 20 percent of unregistered products failed pharmacopeial testing, but only 3 percent of registered ones failed (Wondemagegnehu, 1999).

Antimalarials in Southeast Asia and sub-Saharan Africa There is consistent survey evidence that antimalarial drugs, medicines bought around 200 million times per year, mostly for children under the age of 5, are often of poor quality (WHO, 2011b). The demand for these drugs is highest in sub-Saharan Africa and Southeast Asia, which together account for 94 percent of malaria cases (WHO, 2011b). Acute malaria episodes come on quickly and often; antimalarials are bought on short notice from the most

[3] Including, but not limited to, amoxicillin, ampicillin, chloroquine, rifampicin, and co-trimoxazole.

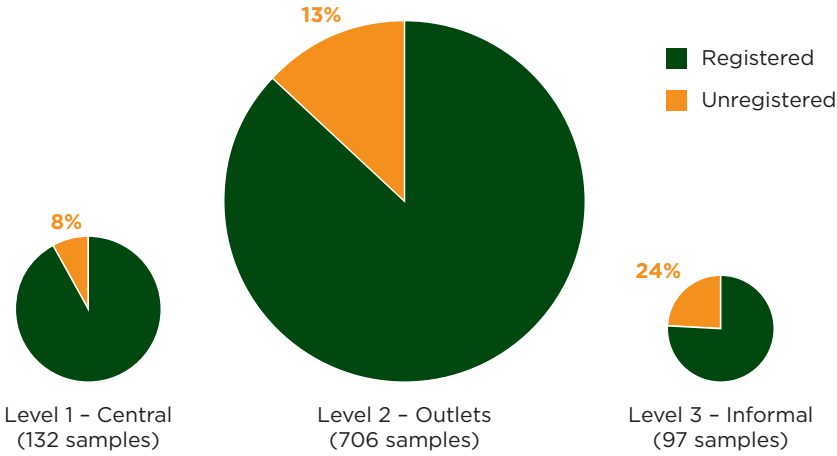

FIGURE 3–4 Registration status of antimalarial samples by distribution level.
SOURCE: WHO, 2011a.

convenient vendor. For these reasons, they are often the target of criminals and unscrupulous manufacturers.

A WHO study of antimalarial drug quality in six African countries[4] used a stratified convenience sample (WHO, 2011a). In the spring of 2008, regulatory agency staff in the six countries collected samples from central stores, licensed outlets, and unlicensed markets (WHO, 2011a). Investigators screened all samples in the field and sent a subset for full quality-control testing (WHO, 2011a). Investigators found unregistered medicines least often at the central distribution level (see Figure 3-4). Quality analysis on a subset of products found no evidence that the unregistered drugs were of lower quality than the registered ones (see Figure 3-5) (WHO, 2011a).

Field screening of 893 samples detected ingredient failures in 12 percent (WHO, 2011a). Of the 267 samples selected for full quality-control testing, 28 percent failed (see Figure 3-6) (WHO, 2011a).

The WHO study findings are cause for concern, especially as they sampled heavily from national central medicine stores, the most controlled setting. A recent review paper includes some higher estimates of poor-quality antimalarial drugs (Nayyar et al., 2012). The review included 28 published and unpublished studies, mostly (n = 22) from convenience samples, but also 7 that included some type of randomized design (Nayyar et al., 2012).

[4] Cameroon, Ethiopia, Ghana, Kenya, Nigeria, and Tanzania.

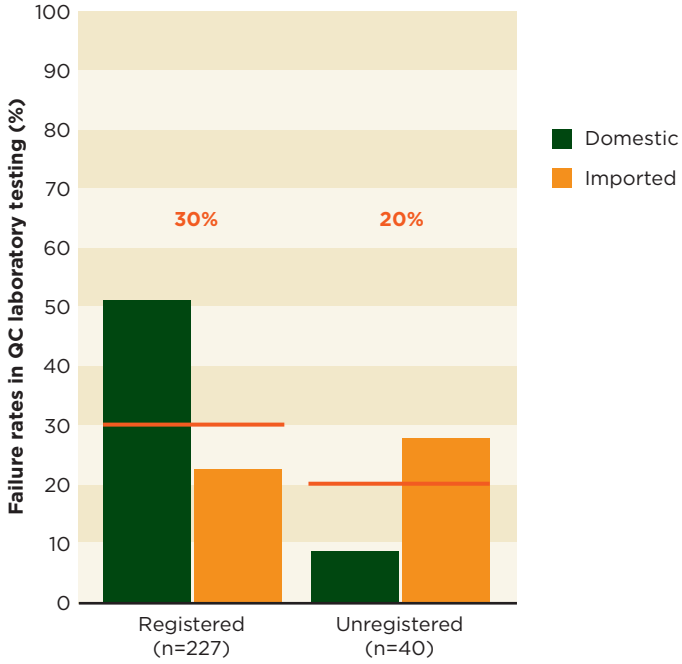

FIGURE 3–5 Quality failures of registered and unregistered antimalarials in 267 samples.

NOTE: QC = quality control.

SOURCE: WHO, 2011a.

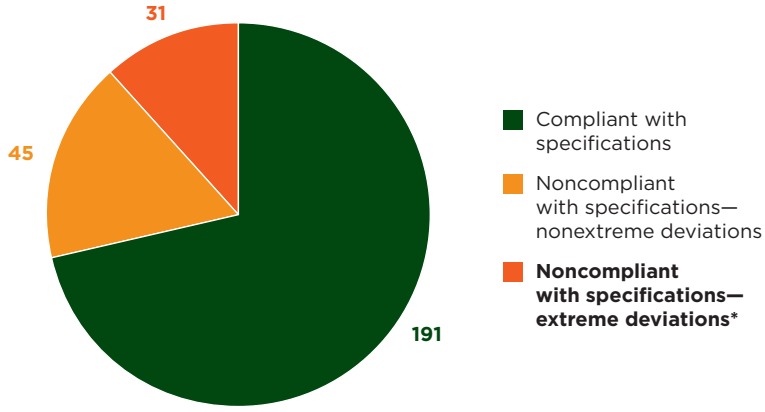

FIGURE 3–6 Results of full quality-control analysis in 267 samples.

*In this survey, extreme deviations were defined as a deviation by at least 20% from the declared content of one or more active ingredients, and/or dissolved percentage of one or more active ingredients less than the pharmacopoeial limit (Q) minus 25%.

SOURCE: WHO, 2011a.

Of 1,437 samples from Southeast Asia, 35 percent (n = 497) failed chemical testing. Of the 497 samples that failed chemical testing, 34 percent had no active ingredient; 4 percent had low active ingredient. In a subset of 919 samples with intact packaging and a verified, genuine packaging sample for comparison, 46 percent failed packaging analysis (Nayyar et al., 2012). Investigators classified all drugs failing packaging analysis as falsified, as well as those substandard drugs that contained no active ingredient or an ingredient not listed on the label (Nayyar et al., 2012). They classified 36 percent of 1,260 eligible samples as falsified.

Nayyar and colleagues used the same criteria to categorize samples from sub-Saharan African countries (Nayyar et al., 2012). Thirty-five percent (n = 796) of 2,297 samples failed chemical analysis. Forty-five percent of the studies reported active ingredient test results, finding that 121 (15 percent) had low active ingredient and 3 percent had excessive active ingredient (Nayyar et al., 2012). Only one study reported packaging analysis, and it found 36 percent failure (Nayyar et al., 2012). Nayyar and colleagues had fewer African samples (n = 389) from which to calculate the percentage of falsified drugs; they found 20 percent falsified (see Table 3-7) (Nayyar et al., 2012).

A consistent problem with all convenience surveys of drug quality is that they tend to sample heavily from the formal market: licensed pharmacies and dispensaries. Results of these studies will likely underestimate the burden of falsified and substandard drugs in places where much of the population buys essential medicines in unregulated bazaars. Sampling from these vendors is difficult, but a convenience sample of informal and private medicine sellers in Guyana and Surinam found 58 percent of the antimalarial samples from Guyana and all the samples from Surinam to be falsified or substandard (Evans et al., 2012). In a Burkina Faso study, Tipke and colleagues compared antimalarial drug quality in licit and illicit vendors. They found that 90 percent of samples from street vendors and open markets were substandard, and only 10 percent of samples from legal vendors were substandard (Tipke et al., 2008).

SYSTEMATIC RANDOM SAMPLES OF DRUG QUALITY

Drug quality is a global problem. Research estimating the precise extent of this problem is hard to find. There are few epidemiologically rigorous surveys of drug quality. This section presents the results of a few population-based random surveys of drug quality.

Kaur and colleagues analyzed antimalarial quality in drugs drawn from a systematic, random sample of a range of Tanzanian retail outlets, including drug stores, general stores, street hawkers, and medicine kiosks

Key Findings and Conclusions

- Few published studies use systematic random samples to estimate the burden of falsified and substandard drugs.
- Those that do indicate serious problems with antimalarial, antibiotic, and antituberculosis drugs in sub-Saharan Africa and Southeast Asia.
- Adherence to the Medicine Quality Assessment Reporting Guidelines would improve understanding of the problem.

(Kaur et al., 2008). Investigators stratified districts according to their participation in a national bed net program, chose districts at random from among the strata, and then surveyed 30 percent of wards in each study district (Kaur et al., 2008). They divided wards into major and nonmajor trading centers and drew half the samples from each type of market (Kaur et al., 2008). Between May and September 2005, investigators collected 1,080 samples from 2,474 vendors, one from each store that had them in stock on the day of the study visit (Kaur et al., 2008). After excluding 166 expired samples and 32 with no labeled expiry date, investigators had 882 samples, from which they systematically chose 301 for chemical analysis (Kaur et al., 2008); 12.2 percent failed quality testing (Kaur et al., 2008).

An older study in West Africa found more widespread quality problems. Taylor and colleagues collected 581 drugs from 35 randomly selected registered pharmacies in urban Nigeria (Taylor et al., 2001). They found 42 percent of antimalarials, 41 percent of antibacterials, and 54 percent of antituberculosis drugs outside of British Pharmacopoeia limits (Taylor et al., 2001). A stratified random sample of medicine shops and licensed pharmacies in Laos found 90 percent of artesunate samples failed quality testing (Sengaloundeth et al., 2009).

Researchers in southeast Nigeria attempted to include unlicensed private medicine dealers in their sample of antimalarial drug quality (Onwujekwe et al., 2009). They collected samples of a range of antimalarials from patent medicine dealers, pharmacies, public and private hospitals, and primary health care centers (Onwujekwe et al., 2009). Thirty-seven percent of drugs tested failed to meet U.S. Pharmacopeia specifications, by either not containing the active ingredient listed or containing it in low doses (Onwujekwe et al., 2009). Among the failed samples, 60 percent came from low-level shops, mostly the patent-medicine shops (Onwujekwe et al., 2009).

Malaria medicine dispensed at a clinic in Sittwe, Burma.
SOURCE: Paula Bronstein/Getty Images.

Though most epidemiologically rigorous research on drug quality has tested antimicrobial drugs, there is some information about other essential medicines. In a 2012 study, Stanton and colleagues prepared an exhaustive sampling frame of formal and informal drug sellers in three districts in Ghana (Stanton et al., 2012). They chose 75 vendors at random from the sampling frame, from which patient actors collected 101 samples of ergometrine and oxytocin, the thermally unstable, uterotonic drugs used to treat postpartum hemorrhage (Stanton et al., 2012). A total of 89 percent of samples failed pharmacopeial testing; none of the ergometrine samples and only 26 percent of oxytocin samples met pharmacopeial specifications (Stanton et al., 2012). All oxytocin samples (n = 46) were from unregistered manufacturers, though 18 were from manufacturers with registration pending; 69 percent of ergometrine samples (n = 38) came from unregistered manufacturers, though 11 were from manufacturers with registration pending (Stanton et al., 2012). All unregistered samples failed quality testing (Stanton et al., 2012).

A Need for More Field Surveys

The best estimates of the scope of the drug supply affected come from systematic, random sampling and testing of medicines drawn from a rep-

resentative cross section of the market. Such studies are uncommon (Seear, 2012). The expense of required assays, discussed further in Chapter 6, is one barrier, but a large part of the problem is logistical. The first step in drawing a systematic random sample of drugs is identifying the sampling frame, the list of every drug vendor in a given area. In developed countries, registered pharmacies and dispensaries are the only place most of the population gets medicine. In low- and middle-income countries, however, there is often an extensive pharmaceutical gray market. Identifying all the vendors is difficult and can be further complicated by the blurry lines between licit and illicit commerce (Seear et al., 2011). Health workers may supplement their incomes by selling medicine informally (Peters and Bloom, 2012); peddlers may trade medicines occasionally, along with any number of dry goods, at bazaars and flea markets. Without formative research to catalogue the sampling frame, research on medicines quality is vulnerable to bias.

There is also opportunity for bias in sample collection. Samples should be bought by patient actors, local study staff posing as shoppers who conceal from the vendor that they are working on an epidemiological investigation.

Without taking steps to protect study validity, the researchers risk wasting time and money on a study that does not produce reliable estimates. For example, in 2009 the Indian government conducted a massive survey of drug quality across the country, estimating that only 0.04 percent of drugs are substandard (CDSCO, 2009). Questions about the methodological rigor of the survey, particularly the choice of sampling frame and methods for sample collection, have called these results into question both within India and internationally (Bate, 2009, 2010; Pandeya, 2009).

The committee supports the guidelines on field surveys of medicine quality that Newton and colleagues proposed in March 2009 (Newton et al., 2009). They provide a standard protocol for collecting medicines samples and concrete advice on sampling techniques (Newton et al., 2009). More research adhering to the checklist in Table 3-8 would allow for a better understanding of the burden of falsified and substandard drugs, and it would facilitate valid comparisons of the problem among countries and over time.

GLOBAL PREVALENCE ESTIMATES

The committee believes that more research in adherence with the guidelines put forth in Table 3-8 would give a better understanding of where and to what extent falsified and substandard medicines circulate. There is no substitute, however, for pharmacovigilance and postmarket surveillance. It is not a coincidence that falsified and substandard medicines circulate

Key Findings and Conclusions

- Falsified and substandard medicines circulate in countries where there are not sufficient systems to monitor drug safety and adverse events.
- There are currently no accurate estimates of the global burden of falsified and substandard drugs. This lack of clarity impedes coordinated international action.
- The WHO rapid alert system is a promising program to track falsified and substandard drugs in low- and middle-income countries.

in countries where there are not sufficient systems to monitor drug safety and adverse events. A 2012 IOM report called for greater international investment in low- and middle-income-country surveillance systems (IOM, 2012). The committee agrees with this report, especially the call for technical support for surveillance tools and protocols (IOM, 2012). National surveillance systems should work to detect signals of substandard and falsified drugs. Incorporating pharmacovigilance into the broader public health surveillance system will help ensure the system's survival.

Recommendation 3-1: Governments should establish or strengthen systems to detect substandard, falsified, and unregistered medicines. This surveillance should be integrated with established public health surveillance systems. Analysis and reporting should precisely describe the product's quality, packing, and registration.

As Chapter 4 explains, governments can be slow to act against falsified and substandard medicines. In emerging economies, officials may see enforcing drug quality standards as at odds with building the nascent manufacturing sector (IOM, 2012). It is also difficult to promote international effort against a threat as amorphous as fake medicines. Concrete data spur politicians and policy makers to action—information such as the number of doctor's appointments repeated because of falsified and substandard drugs, the number of hospital beds taken by victims of pharmaceutical crimes, premature deaths from untreated disease, and productive years lost to society from medicine poisoning. Pharmacovigilance is the first step to generating the needed data. When pharmacovigilance systems indicate lack of medicines' efficacy, these signals should be followed. In-depth investigations can eventually produce data on the specific consequences of falsified and substandard medicines.

TABLE 3–8 Medicine Quality Assessment Reporting Guidelines

Section and Topic	Item	Description
Title/abstract/keywords	1	• Identify the article as a study of medicine quality • Provide an abstract of what was done and what was found, describing the main survey methods and chemical analysis techniques used
Introduction	2	• Summarize previous relevant drug quality information and describe the drug regulatory environment • State specific objectives
Methods		
Survey details	3	The timing and location of the survey; when samples collected and when samples analyzed
Definition	4	The definitions of counterfeit, falsified, substandard, and degraded medicines used
Outlets	5	The type, including indices of size (e.g., turnover), of drug outlets sampled
Sampling design	6	• Sampling design and sample size calculation • Type and number of dosage units purchased/outlet • Definition of sampling frame • Question of interest, assumptions, sampling method(s) (including method of randomization if random sampling used)
Samplers	7	Who carried out the sampling and in what guise? What did the collector say in buying the medicines?
Statistical methods	8	Describe the data analysis techniques used
Ethical issues	9	Whether ethical approval was sought and whether the study encountered any ethical issues
Packaging	10	Packaging examination and reference standards
Chemical analysis	11	Chemical analysis and dissolution testing procedures and location(s) of laboratory. Description of validation and reference standards used
Method validation	12	Details of laboratory method validation results, including but not limited to: certificate of analysis for reference standard, within and between run repeatability (RSD% for n = 5–8), detection and quantization limits, accuracy observed for reference samples, linear range for all analytes, sample preparation recovery studies, selectivity. Possibly, validation against a reference method or inter-laboratory study

continued

TABLE 3–8 *Continued*

Section and Topic	Item	Description
Blinding	13	Whether chemistry was performed blinded to packaging and vice versa
Results		
Outlets	14	The details of the outlets actually sampled, class of pharmacy (e.g., public, private for profit, private not for profit, informal, itinerant)
Missing samples	15	The reasons why any outlets chosen for sampling did not furnish a sample. Do these outlets differ systematically from those in which samples were obtained?
Packaging and chemical results	16	• Packaging and chemistry results and their relationship • Details of products sampled—how many, in what drug classes, countries of origin, batch numbers, manufacture and expiry dates • Results for each analysis—packaging, % active ingredient, dissolution • Additional information could be included in supplementary material
Category of poor-quality medicine	17	A clear statement for each medicine sample detected, whether the investigators class it as genuine, counterfeit, substandard, or degraded, with an explanation as to why and whether the medicine was registered with the government in the location(s) sampled
State company and address as given on packaging	18	If the names of companies and addresses are not given, give a reason as to why this information is not provided.
Sharing data with the regulatory authority	19	Whether the data shared with the appropriate regulatory agency
Dissemination	20	Description of any noncovert packaging features that would allow others to detect counterfeit medicines. If publication is not possible, consider disseminating via web-based supplementary material.
Discussion		
Key Results	21	Summarize key results with reference to study objectives
Limitations	22	Discussion of limitations of study, especially how robust the estimates of prevalence are and how applicable they may be to wider geographical areas. Discuss the direction and extent of any potential bias.

TABLE 3–8 *Continued*

Section and Topic	Item	Description
Interpretation	23	An interpretation of the results, in conjunction with prior studies, in relation to public health
Intervention	24	Whether interventions are thought appropriate and, if so, what type
Other information		
Conflict of interest	25	State any potential conflicts of interest.
Funding	26	Give the source of funding and role of funders in the study.

NOTE: RSD = relative standard deviation.

SOURCE: Newton et al., 2009.

There is some reason to suspect problems with unregistered medicines in developing countries, but these problems resist detection (Amin et al., 2005). Postmarket surveillance systems, by definition, follow only those products registered and granted market authorization in a given country. The committee believes that unregistered medicines are as important a surveillance target as falsified and substandard ones. Research on the quality of unregistered medicines indicates that they are often of poor quality (Bate et al., 2010; Lon et al., 2006; Stanton et al., 2012; Wondemagegnehu, 1999). Furthermore, drugs for sale in a country where they are not registered have often been trafficked. Chapter 5 will explain why any product that has left the licit chain of custody is suspect.

A complete picture of the magnitude of the problem of poor-quality medicines depends on thorough and novel surveillance. This surveillance should advance systematic investigation of drug quality failures to build evidence for changing policy. The WHO is developing such a system and training surveillance staff in 10 counties on its use. The committee sees great promise in this system for other developing countries.

The WHO Global Capacity-Building Project

There are currently no accurate estimates of the global burden of falsified and substandard drugs. This lack of clarity hinders coordinated international action. Evidence suggests, however, that the problem is most common in low- and middle-income countries. Unscrupulous manufacturers and criminal cartels take advantage of the comparatively weak drug regulatory systems in these countries, knowing that the regulators are

A pharmacy in Macau advertises safe drugs.
SOURCE: Mark Obusan/Getty Images.

poorly equipped for surveillance or enforcement. A recent WHO project attempts to correct this problem by building a "coordinated, continuous, and ongoing global surveillance and monitoring system" for falsified and substandard drugs (WHO, 2012b, p. 11). The committee believes this project is promising for the 10 countries[5] participating in the pilot program and, eventually, for the world.

The system makes use of rapid alert forms—Excel spreadsheets with mandatory fields and detailed guidance in dropdown menus (personal communication, Michael Deats, WHO, October 12, 2012). The investigator

[5] Cambodia, Croatia, Georgia, Indonesia, Kyrgyzstan, Malaysia, the Philippines, Russia, Ukraine, and Vietnam.

TABLE 3–9 Information Collected in the WHO Rapid Alert System

Rapid Alert	Details
Reporting person	Contact details
Suspect product details	Full details of all suspect products (up to 30 per report)
How suspect product was discovered	Regulated or unregulated supply chain
Product analysis	Laboratory results on medicine and packaging
Photographs	Photographs of product, packaging, method of concealment
Impact on public health	Record of adverse reactions in patients
Action Taken	**Details**
Communication	Details of recall or public announcements
Dissemination	Record of those other organizations, member states, or stakeholders informed
Investigation	Details of agencies involved in investigating the case
Comments	Specifically what aroused suspicion concerning the product

NOTE: WHO = World Health Organization.

SOURCE: Personal communication, Michael Deats, WHO, October 12, 2012.

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who finds an illegitimate drug completes the form and sends it to WHO headquarters, copying regional and country offices. At the WHO, the spreadsheet data populate a master database. Receipt of the form triggers a follow-up contact from a WHO investigator, who queries the reporter on the drug's packaging, registration, and physical and chemical attributes and if the incident might be connected to other criminal activity (personal communication, Michael Deats, WHO, October 12, 2012). Table 3-9 shows more detail about the data collected in the rapid alert form.

Regulators from the 10 pilot countries testing the rapid alert form and incident investigation system had training on the system in September 2012. The pilot testing ran until December 2012 (personal communication, Michael Deats, WHO, October 12, 2012). Already the system has allowed investigators to link incidents in multiple countries. Eventually, regulators may link falsified and substandard reporting to national pharmacovigilance systems, which would give more depth to information about lack of efficacy (personal communication, Michael Deats, WHO, October 12, 2012).

The lack of consensus on how to define falsified and substandard medicines has held back all public action on the topic, even surveillance.

The WHO project gets around this problem by recording problems with medicines and by not attempting to make the observed problems fit the confusing and contradictory national definitions of substandard, falsely labeled, spurious, counterfeit, etc.

Patient reporting triggers most investigations in the pilot countries. This depends on motivated and knowledgeable patients, and a longer-term improvement to the project might aim to increase reporting from health workers. However, Michael Deats, the WHO technical officer in charge of the program, explained that while he was working as a regulator in Britain, some of his best leads came from patients, especially ones who take medication for chronic disease. One informant was a patient in the habit of rubbing his pill in his hand before taking it and was immediately suspicious when the color rubbed off (personal communication, Michael Deats, WHO, November 11, 2012). A similar signal came from a patient accustomed to cutting his pills in half, who noticed irregular friability when he cut them (personal communication, Michael Deats, WHO, November 11, 2012).

The committee recognizes that building surveillance systems will be challenging in many countries. Nevertheless, taking steps to establish a system or to strengthen the existing system is a reasonable first step in most of the world. Developing countries may benefit from momentum for building surveillance among donor governments and international organizations (IOM, 2012). The WHO is also encouraging action in the same direction. At a meeting in November 2012, representatives of 200 member states agreed to develop instruments to more accurately measure the burden of substandard and falsified drugs (WHO, 2012c). To this end, the WHO capacity-building project is testing and developing surveillance tools specifically for use in low- and middle-income countries. As the pilot project goes on, the regulators and WHO staff may identify revisions that make the protocol more accessible in poor countries.

The WHO monitoring format advances understanding of the scope of the problem without depending on common variable names. The committee sees the WHO rapid alert system as an uncommonly thorough and precise tool for data collection. These data will inform tailored drug quality programs. For example, if the data indicate that substandard medicines are the main drug quality problem in one part of the world, then better regulation of manufacturers can do much to improve the problem. Similarly, if it becomes clear that a country has a problem with diverted medicines in commerce, then some of the distribution chain improvements presented in Chapter 5 would enhance the national drug safety program. Consistent use of this rapid alert form and eventually linking it to national pharmacovigilance systems would advance international discourse and give a more nuanced understanding of the extent and type of falsified, substandard, and unregistered medicines that circulate around the world.

TABLE 3–5 The Pharmaceutical Security Institute's 2011 Open-Source Review

Country	Action	Justification[a]	Quantity	Therapeutic Category	Drugs	Value	Arrests
Afghanistan	Destroyed	Substandard & expired	32 tons	Unknown	Unknown	$-	0
Angola	Seized-arrests	Illegal	1,000 kilos	Unknown	Unknown	$-	419
Bangladesh	Arrests	Counterfeit	Unknown	Unknown	Unknown	$-	2
Brazil	Seized	Diverted		Cytostatic, metabolism	Cancer and transplant	$120,000	0
Brazil	Sentence	Counterfeit	$2.5 million in damages	Unknown	Androcur	$-	0
Brazil	Seized	Counterfeit	46,688 dosage units	Multiple	Multiple	$-	0
Brazil	Seized	Unknown	168 seizures	Unknown	Unknown	$-	0
Canada	Seized-arrests	Counterfeit	100,000 dosage units	Genitourinary	ED	$1,000,000	1
Chile	Seized-arrests	Illegal	12,000 dosage units	CNS	Psychotropic	$-	2
China	Destroyed	Counterfeit & substandard	60 tons	Genitourinary, metabolism	ED & diabetes	$6,000,000	0
China	Sentence	Counterfeit		Cytostatic	Oncology	$-	1
China	Sentence	Counterfeit		Cytostatic	Oncology	$-	11
China	Seized-arrests	Counterfeit		Unknown	Unknown	$3,000,000	263
China	Seized-arrests	Counterfeit	6,900,000 dosage units	Genitourinary	ED	$-	15
China	Seized-arrests	Counterfeit	201 types of drugs	Unknown	Unknown	$-	23
China	Seized-arrests	Counterfeit		Unknown	Unknown	$314,000,000	1,770

continued

TABLE 3–5 *Continued*

Country	Action	Justification[a]	Quantity	Therapeutic Category	Drugs	Value	Arrests
China	Sentence	Counterfeit		Unknown	Unknown	$-	1
China	Seized-arrests	Counterfeit		Unknown	Unknown	$29,884,160	114
China	Sentence	Counterfeit	840,000 dosage units	Unknown	Unknown	$4,720,000	8
China	Seized-arrests	Counterfeit		Unknown	Unknown	$33,000,000	121
China	Seized	Counterfeit	800 boxes, 121 types of drugs	Unknown	Unknown	$253,440	0
China	Seized-arrests	Illegal	14,000 dosage units	Hormones	Abortion	$-	1
Colombia	Seized	Adulterated & expired	7.5 tons	Unknown	Unknown	$-	0
Colombia	Sentence	Unknown		Unknown	Unknown	$-	288
Colombia	Seized	Illegal	436,180 dosage units	Unknown	Unknown	$-	0
Colombia	Seized-arrests	Counterfeit	150,000 dosage units	Cytostatic, anti-infective	Cancer & HIV/AIDS	$-	22
Cyprus	Seized	Counterfeit & illegal	7,500 dosage units	Unknown	Unknown	$-	0
Czech Republic	Seized-arrests	Counterfeit	Unknown	Hormones	Anabolic steroids	$-	11
Dominican Republic	Seized-arrests	Adulterated		Unknown	Unknown	$31,000	3
Ghana	Arrest	Illegal		Anti-infective	Antimalarial	$-	1
Ghana	Arrest	Illegal		Anti-infective	HIV/AIDS	$-	0
Ghana	Detection	Illegal		Anti-infective	Antimalarial	$-	0

India	Seized-arrests	Counterfeit	32 packs	Unknown	Blood glucose test strips	$-	3
India	Seized-arrests	Counterfeit	250,000 dosage units	Respiratory	Coscold (cough tablets)	$-	3
India	Arrests	Counterfeit		Unknown	Glucose-D	$-	3
India	Seized-arrests	Counterfeit		Unknown	Unknown	$74,800	3
India	Seized-arrests	Counterfeit	600 boxes	Unknown	Crocin suspension	$-	2
India	Seized-arrests	Counterfeit		Unknown	Unknown	$5,610	5
India	Arrests	Unknown		Unknown	Unknown	$-	4
India	Seized	Spurious	388,000 dosage units	Anti-infective	Antibiotics	$-	0
India	Arrests	Unknown		Unknown	Unknown	$-	4
India	Seized-arrests	Spurious & contraband		Unknown	Unknown	$48,620	2
India	Seized-arrests	Illegal		CNS	Psychotropic	$4,114,072	10
India	Seized	Counterfeit		Unknown	Unknown	$233,754	0
Indonesia	Seized	Illegal		Unknown	Unknown	$8,899	0
Israel	Seized-arrests	Counterfeit	230,000 dosage units	Metabolism, genitourinary	Weight loss & ED	$-	1
Israel	Sentence	Unknown		Genitourinary	ED	$-	1
Israel	Seized	Counterfeit	100,000 dosage units	Genitourinary	ED	$-	0
Kenya	Detection	Counterfeit	1,340 batches	Anti-infective	HIV/AIDS	$-	0
Lebanon	Seized-arrests	Counterfeit	200 large boxes	Unknown	Unknown	$-	2
Mexico	Theft	Stolen	98 cases	Unknown	Unknown	$-	0

continued

TABLE 3–5 *Continued*

Country	Action	Justification[a]	Quantity	Therapeutic Category	Drugs	Value	Arrests
Mozambique	Seized-arrests	Diverted		Anti-infective	HIV/AIDS	$5,200	9
Nigeria	Seized	Illegal		Anti-infective	Antimalarial	$-	0
Nigeria	Seized	Counterfeit & unregistered	844 cartons	Unknown	Unknown	$1,906,577	0
Nigeria	Arrest	Illegal		Unknown	Unknown	$-	0
Nigeria	Seized	Counterfeit		Unknown	Unknown	$-	0
Nigeria	Seized	Illegal		Unknown	Unknown	$-	5
Nigeria	Seized	Illegal		Unknown	Unknown	$-	0
Nigeria	Arrests	Illegal		Unknown	Unknown	$-	30
Nigeria	Seized	Illegal		Anti-infective	Antibacterial	$1,900	0
Nigeria	Detection	Counterfeit		Unknown	Unknown	$12,710	0
New Zealand	Arrests	Unknown		Unknown	Unknown	$-	1
Pakistan	Charged	Unlicensed & spurious		Unknown	Unknown	$-	0
Pakistan	Arrests	Spurious & substandard		Unknown	Unknown	$-	1
Pakistan	Seized-arrests	Counterfeit		Anti-infective	Antibiotics	$-	3
Pakistan	Charged	Spurious		Unknown	Unknown	$-	0
Pakistan	Arrests	Spurious & unauthorized		Unknown	Unknown	$-	4
Pakistan	Sentence	Spurious & substandard		Unknown	Unknown	$-	1

Pakistan	Seized	Spurious		Anti-infective	Vaccine	$-	0
Pakistan	Seized-arrests	Counterfeit		Anti-infective	Antibiotics	$220,535	12
Pakistan	Charged	Spurious & substandard		Unknown	Unknown	$-	11
Peru	Seized	Unknown	15,000 dosage units	Unknown	Unknown	$7,000	0
Peru	Destroyed	Adulterated & expired	22 tons	Unknown	Unknown	$7,000,000	0
Philippines	Seized	Counterfeit	1,000 boxes	Genitourinary	ED	$70,375	0
Portugal	Seized	Unknown	133,000 dosage units	Genitourinary, metabolism	ED & weight loss	$-	0
Russia	Seized	Illegal	2.9 million counterfeited goods	Unknown	Unknown	$-	0
Singapore	Seized	Illegal		Metabolism, hormones	Weight loss & birth control	$10,896	0
Slovakia	Seized	Counterfeit	128,000 dosage units	Hormones, genitourinary	Steroids & ED	$-	0
South Korea	Charged	Counterfeit		Genitourinary	ED	$-	15
Spain	Seized-arrests	Counterfeit & illegal	710,000 dosage units	Hormones, genitourinary	Steroids & ED	$-	26
Spain	Seized-arrests	Illegal	23,000 dosage units	Hormones	Anabolic steroids	$-	1
Taiwan	Seized-arrests	Counterfeit & illegal		Metabolism, genitourinary	Weight loss & ED	$-	168
Tanzania	Detection	Illegal		Anti-infective	Antibiotics & antimalarial	$-	7

continued

TABLE 3–5 *Continued*

Country	Action	Justification[a]	Quantity	Therapeutic Category	Drugs	Value	Arrests
Thailand	Seized-arrests	Counterfeit		Metabolism	Weight loss	$969,932	10
Thailand	Seized-arrests	Illegal		CNS, genitourinary	Sleeping & ED	$3,233	2
UAE	Seized	Illegal	1,000,000 dosage units	Genitourinary	ED	$-	0
UAE	Arrest	Illegal	70,000 dosage units	Genitourinary	ED	$-	0
Uganda	Detection	Counterfeit		Anti-infective	Anti-malarial	$6,072	0
UK	Sentence	Counterfeit & illegal	Unknown	Genitourinary	ED	$-	1
UK	Sentence	Illegal	Unknown	Hormones, genitourinary	HGH & ED	$-	1
UK	Seized	Counterfeit & illegal	8.5 million dosage units	Genitourinary	ED	$-	0
UK	Seized-arrests	Counterfeit & illegal		Unknown	Unknown	$1,615,600	3
UK	Sentence	Counterfeit		Genitourinary	ED	$-	5
UK	Sentence	Counterfeit	896,000 dosage units	Multiple	Multiple	$-	1
UK	Sentence	Counterfeit		Genitourinary	ED	$-	2
UK	Sentence	Counterfeit	800 dosage units	Respiratory	Inhalers	$-	1
UK	Arrest	Illegal		CNS	Pain management	$-	1
UK	Sentence	Counterfeit		Genitourinary	ED	$-	1
UK	Sentence	Stolen		Multiple	Multiple	$-	1
UK	Seized	Counterfeit & illegal	1.2 million dosage units	Multiple	Multiple	$-	0

UK	Sentence	Illegal	6,100 dosage units	Genitourinary	ED	$-	1
UK	Sentence	Conspiracy		Unknown	Unknown	$-	1
Vietnam	Seized-arrests	Counterfeit	1,000 dosage units	Genitourinary	ED	$-	2
West Africa	Seized-arrests	Counterfeit & illicit	10 tons	Unknown	Unknown	$-	100
					Totals:	**$408,324,203**	**3,547**

NOTES: $- = value unknown; CNS = central nervous system; ED = erectile dysfunction; HGH = human growth hormone; UAE = United Arab Emirates; UK = United Kingdom.
[a] As noted in footnote *a* under Table 3-2, PSI uses the term *counterfeit* broadly, in accordance with a WHO definition. See page 89. The organization's open-source review presents each case as it is in the open source.
SOURCE: PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012.

TABLE 3–6 Major Studies of Falsified and Substandard Antibiotics, 1996-2006

Author (year)	No. of Drugs Analyzed	Country	Category of Drugs Studied	Method of Detection of Counterfeit or Substandard Drug
Hu et al. (2006)	Not reported	China	Macrolides: erythromycin, clarithromycin, roxithromycin, azithromycin, erythromycin ethylsuccinate, kitasamycin, leucomycin A_3, acetylspiramycin, acetyl-kitasamycin, midecamycin and meleumycin	FCIS consisting of two color reactions based on functional groups in molecules of macrolide antibiotics and two TLC methods were developed for screening of fake macrolide drugs.
Kayumba et al. (2004)	33	Rwanda and Tanzania	Essential antimicrobials (amoxicillin capsules, metronidazole tablets, TMP–SMX tablet)	Commercially available drug formulations, USP 24 dissolution tests, HPLC.
Syhakhang et al. (2004)	300	Laos	Ampicillin, tetracycline	HPLC, potentiometric titration, and ultraviolet spectrophotometry. The identity was confirmed by TLC, UV, or color reactions.

Results	Characteristics of Counterfeit or Substandard Drugs	Pharmaceutical Companies Involved or Country of Manufacture
Two lots of capsules and one lot of granule had no active ingredients imitating erythromycin ethylsuccinate capsule and azithromycin granule, respectively, one lot of erythromycin tablets imitating roxithromycin tablets, and two lots of meleumycin capsule imitating midecamycin capsule.	No active ingredient, wrong ingredient, no color change in sulphuric acid reaction	China
At the time of purchase, the drug content of all the formulations was within the limits recommended by the USP 24, but after 6-month storage, the drug content of one sulfamethoxazole/trimethoprim was found to be substandard. Immediately after purchase, four formulations (three sulfamethoxazole/trimethoprim and one sulfadoxine/pyrimethamine combination) failed the USP 24 dissolution test. Except for three metronidazole, dissolution tests performed after 6 months of storage under simulated tropical conditions showed that drug release remained within the USP 24 recommended values. In total, 24% of the sampled formulations (8/33) failed the dissolution test.	Poor in vitro drug release profiles and dissolution (four formulations [three sulfamethoxazole/trimethoprim and one sulfadoxine/pyrimethamine combination]). Some of the formulations tested were not stable in terms of drug content (one sulfamethoxazole/trimethoprim) and dissolution (three metronidazole formulations), upon storage under simulated tropical conditions.	TPI (metronidazole), Holden Medica (metronidazole), Labophar (TMP–SMX, sulfadoxine and pyrimethamine), Shalina (sulfamethoxazole), ACE (TMP–SMX). Rwanda and Tanzania.
The percentage of substandard drugs decreased significantly from 46% to 22% (66 out of 300) between 1997 and 1999 ($P < 0.001$). Substandard ampicillin and tetracycline were reduced significantly from 67% to 9% and from 38% to 12%, respectively ($P < 0.001$). In total, 3% versus 1% contained no active ingredient, 12% versus 4% had too little or too much active ingredient and 35% versus 14% had weight variation outside pharmacopoeial limits.	No active ingredient (ampicillin and tetracycline), too little (ampicillin) or too much (tetracycline) active ingredient, weight variation outside pharmacopoeial limits	24% (23 out of 97) of the drugs from Lao factories, 17% (24 out of 143) of the drugs from Thailand and 47% (17 out of 36) of the drugs of unknown origin were substandard.

continued

TABLE 3–6 *Continued*

Author (year)	No. of Drugs Analyzed	Country	Category of Drugs Studied	Method of Detection of Counterfeit or Substandard Drug
Prazuck et al. (2002)	21	Northern Myanmar	Antimicrobials (benzathine benzylpenicillin, ceftriaxone, chlortetracycline, ciprofloxacin, TMP–SMX doxycycline and erythromycin)	Drug quantitative analysis was performed with titrimetry and visible UV spectrophotometry. Qualitative analysis was performed with TLC.
Taylor et al. (2001)	581	Nigeria	Antibacterial and antituberculosis drugs	HPLC
Okeke and Lamikanra (2001)	5	Nigeria	Five samples of ampicillin capsules	
Laserson et al. (2001)	71	Colombia, Estonia, India, Latvia, Russia, and Vietnam	INH and RIF single and FDC formulations	TLC kit

Results	Characteristics of Counterfeit or Substandard Drugs	Pharmaceutical Companies Involved or Country of Manufacture
Among the 21 different specialty products, only 3 displayed the official "registered" label. Three drugs were expired and the expiration date was not available for six others. One product did not contain the active drug declared (chlortetracycline) and did not show any in vitro activity against bacteria. Seven of 21 products (33%) did not contain the stated dosage (one more than stated dosage and six less than stated dosage). The highest deficit observed was 48% in two products (co-trimoxazole and benzylpenicillin). The dosage was not available for five drugs. As a result, only 8 of 21 products (38%) did not contain the stated dosage of active drug.	Inappropriate labeling, expired drug, no active ingredient (chlortetracycline), reduced active ingredient	Lombisin, Unicorn, China (chlortetracycline), Yong Fong, Myanmar (co-trimoxazole), China (benzylpenicillin), Helm Pharmaceutical GMBH, Hamburg, Germany (benzathine benzylpenicillin), Cadila Lab, Ahmedabad, India, Dr. Reddy's Lab, Bollaram, India (ciprofloxacin), Remedica Ltd, Limassol, Cyprus (erythromycin and doxycycline), ICPA Lab Ltd, Bombay, India (TMP–SMX)
For all groups of drugs, antibacterial and antituberculosis agents, more than 50% failed to comply with specifications. For some individual drug preparations, all samples assayed were within pharmacopoeial limits. These included trimethoprim and sulfamethoxazole tablets. No metronidazole suspension met pharmacopoeial specifications. Several antibacterial preparations contained very low quantities of active ingredient (ampicillin and amoxicillin 24% to 40%), and for five metronidazole suspension preparations, no active ingredient was detected.	Zero (metronidazole suspension), or very low (ampicillin [syrup and capsules], amoxicillin [syrup], pyrimethamine and sulfadoxine [syrup], cloxacillin [syrup and capsules], and ampicillin and cloxacillin [syrup and capsules]) quantities of active ingredient	Most drugs that failed to pass the test were manufactured in countries such as China, Holland, India, Malaysia, Nigeria, Pakistan, Romania, Switzerland, and the United Kingdom or were of unknown origin.
Three of the five (60%) capsule samples from dispensing points were found to be of lower quality than the officially prescribed standards of pharmaceutical quality. The quality lapses observed were sufficient to bring about determinable differences in biological availability.		
Overall, 10% (4/40) of all samples, including 13% (4/30) RIF samples, contained < 85% of stated content. More FDCs (5/24, 21%) than single-drug samples (2/16, 13%) were substandard. Two RIF samples and one INH sample had an extra component.	Reduced content of active ingredient, extra component	Not reported

continued

TABLE 3–6 *Continued*

Author (year)	No. of Drugs Analyzed	Country	Category of Drugs Studied	Method of Detection of Counterfeit or Substandard Drug
Kenyon et al. (1999)	13	Republic of Botswana	FDC antituberculosis (TB) drugs	TLC as a screening method, and UV or LC as confirmation
Pillai et al. (1999)	10 FDC formulations	South Africa	FDC antituberculosis formulations	Not reported
Stenson et al. (1998)	366	Laos	Ampicillin (tablets and capsules) and tetracycline (tablets and capsules)	Three tests were used: identity, assay, and measurement of weight variation. The identity was confirmed by TLC, UV, and color reactions. Titrimetric, UV, and HPLC methods were used for assay. Potentiometric titration method.
Nazerali and Hogerzeil (1998)	789 samples of 26 brands of 13 essential drugs	Zimbabwe	Injectable benzylpenicillin, amoxicillin, ampicillin, doxycycline, phenyl-methoxypenicillin, and tetracycline	Not reported. Drug quality was measured by level of active ingredient as percentage of stated content and by compliance (pass/fail) with assay standards of the British Pharmacopoeia. Drug stability was measured by comparing mean assay values at central and rural levels and by paired analysis of central and rural samples of the same batch.
Shakoor et al. (1997)	96 (81 Nigeria, 15 Thailand)	Nigeria, Thailand	Amoxicillin, tetracycline, TMP–SMX, ampicillin–cloxacillin	HPLC

Results	Characteristics of Counterfeit or Substandard Drugs	Pharmaceutical Companies Involved or Country of Manufacture
All 13 FDCs contained the stated drugs. However, four (31%) were substandard, including two (15%) with low rifampicin content, one (8%) with excessive rifampicin and one (8%) with excessive pyrazinamide. Both FDCs with low rifampicin contained four drugs and failed TLC screening. The FDC with excessive rifampicin was not detected by TLC screening. Using UV as the gold standard, the sensitivity of TLC for low rifampicin was 2/2 (100%) and the specificity was 9/10 (90%).	Reduced (rifampicin) or excess (rifampicin and pyrazinamide) content of active ingredient	Not reported
The maximum serum concentration for rifampicin in 7 of 10 FDC formulations was not found to be bioequivalent to the reference administered as loose (separate) formulations.	The poor relative bioavailability of rifampicin from some FDCs has been documented. The implications for tuberculosis programs are extremely serious and warrant urgent attention.	Not reported
12 (3.3%) out of the 366 drugs contained no active ingredient, 42 (11.5%) had levels of active ingredient outside acceptable limits in assay, 128 (35.0%) had excessive weight variation and 4 (1.1%) were managed badly in the pharmacy, 67% of ampicillin samples and 38% of tetracycline had bad quality.	No active ingredient (ampicillin), low concentration of active ingredient (ampicillin and tetracycline), weight variation outside pharmacopoieal limits (all), bad retail management (ampicillin)	Out of the 61 samples that were found to contain no active ingredient or to be substandard according to the assay, only 37 were labeled. Of these, 20 originated from Laos, 5 from Thailand and 3 from Vietnam, whereas 9 were of unknown origin.
Poor initial quality accounted for problems in injectable ampicillin (2/10 central samples failed, with 87% and 91% content). An aqueous formulation of injectable procaine benzylpenicillin showed moderate instability with 4% (1% to 6%) loss after 4.3 months but the assay remained within pharmacopoeial limits.	Reduced level of active ingredient	Not reported
36% of samples from Nigeria and 40% of samples from Thailand were substandard with respect to British Pharmacopoeia limits. One amoxicillin sample from Nigeria contained no active ingredient at all.	Zero (amoxicillin) or very low (amoxicillin, TMP–SMX, ampicillin–cloxacillin) quantities of active ingredient	The countries of origin were India, Italy, Nigeria, Pakistan, Thailand, and the United Kingdom, but no patterns emerged with respect to quality of product and country of origin.

continued

TABLE 3–6 *Continued*

Author (year)	No. of Drugs Analyzed	Country	Category of Drugs Studied	Method of Detection of Counterfeit or Substandard Drug
Roy (1994)	137 brands	Bangladesh	Ampicillin, TMP–SMX	Not reported
Taylor et al. (1995)	40	Nigeria	Antibacterial capsules and suspensions of amoxicillin	
Santosh et al. (1992)	7 brands	India	Tetracycline: chemical estimation of seven different marketed brands of tetracycline/HCl capsules for tetracycline content	Fluorimetric method

NOTE: The complete references for the studies cited in this table can be found in Kelesidis et al., 2007. Kelesidis and colleagues use the term *counterfeit* broadly, the way this report uses the term *falsified*. See page 23. FCIS = fast chemical identification test; FDC = fixed-dose combination; HCl = ondansetron hydrochloride; HPLC = high-performance liquid chromatography; INH = isoniazid; LC = liquid chromatography; MIC = minimum inhibitory concentration; RIF = rifampicin; TLC = thin layer chromatography; TMP-SMX = trimethoprim-sulfamethoxazole; USP = U.S. Pharmacopeia; UV = ultraviolet spectrophotometry.

SOURCE: Kelesidis et al., 2007. Reprinted with permission from Oxford University Press.

Results	Characteristics of Counterfeit or Substandard Drugs	Pharmaceutical Companies Involved or Country of Manufacture
A significant proportion of a variety of drug preparations was substandard (27%). Ten brands of ampicillin were found to be substandard in this study and 8 of them had already been assessed as substandard by the regulatory authorities. This was also true of the two brands of co-trimoxazole suspension found to be substandard.	It appeared that active ingredients had been deliberately kept below the required levels.	Not reported
Two amoxicillin capsules (0% and 50%) contained ≥50% of the stated amount of active ingredient. Ten other samples outside the British Pharmacopoeia's range had at least 90% or up to 126%.	The reason why British Pharmacopoeia requirements were not met is unknown. Decomposition is not likely to be a major factor (no large amounts of decomposition products found), poor quality assurance probably plays a part but the very small amounts found in some samples point to fraudulent manufacture or tampering.	
Chemical estimation of seven different marketed brands of tetracycline/HCl capsules for tetracycline content showed that six brands were not meeting the pharmacopoeia prescribed standards. The power content of four brands was well below the labeled amount of the standard drug. Comparative analysis of bioavailability of substandard versus standard product indicates that the use of substandard tetracycline products in undernourished subjects may lead to therapeutic failures and/or result in the development of resistant microorganisms.	The dissolution rate and disintegration time of substandard drugs were in accordance with USP specifications. The bioavailability of substandard product as determined from 48 h urinary tetracycline excretion was significantly lower when compared with standard product both in well-nourished and in undernourished subjects. The plasma steady-state concentrations with the substandard product were below the generally recommended MICs, more so in undernourished subjects.	Not reported

TABLE 3–7 Reports of Poor-Quality Antimalarial Drugs by Region in Southeast Asia and Sub-Saharan Africa, 1999-2011

	Location	Date of Sample Collection	Drug Tested	Method of Testing
Southeast Asia				
Newton et al. (2001)	Cambodia, Laos, Myanmar (Burma), Thailand, Vietnam	1999–2000	Artesunate	HPLC, colorimetric testing (fast red dye), packaging analysis
Newton et al. (2008)	Cambodia, Laos, Myanmar, Thailand-Myanmar border, Vietnam	1999–2005	Artesunate	HPLC, colorimetric testing (fast red dye), packaging analysis
Dondorp et al. (2004)	Cambodia, Laos, Myanmar, Thailand, Vietnam	2002–2003	Artesunate, artemether, dihydroartemisinin, mefloquine	HPLC, colorimetric testing (fast red dye), packaging analysis
Lon et al. (2006)	Cambodia	2003	Artesunate, quinine, chloroquine, tetracycline, mefloquine	HPLC, thin layer chromatography, packaging analysis, disintegration analysis
Sengaloundeth et al. (2009)	Laos	2003	Artesunate	HPLC, colorimetric testing (fast red dye), mass spectroscopy, pollen analysis, X-ray diffraction, packaging analysis
U.S. Pharmacopeia (2004)	China	2004	Artesunate, quinine, chloroquine, sulfadoxine-pyrimethamine, mefloquine	HPLC, thin layer chromatography, visual inspection, dissolution analysis
Bate et al. (2009)	India	2008–2009	Chloroquine	Thin layer chromatography, disintegration analysis
Sub-Saharan Africa				
Ogwal-Okeng JO et al. (2003)	Uganda	2001	Chloroquine tablets and injections	HPLC
Basco et al. (2004)	Cameroon	2001	Chloroquine, quinine, sulfadoxine-pyrimethamine	Colorimetric test, thin layer chromatography
Amin et al. (2005)	Kenya	2002	Sulfadoxine-pyrimethamine, amodiaquine	HPLC, dissolution tests

Obtained From	Sampling Technique	Total Sample Tested	Samples That Failed Testing		Falsified*
			Chemical Assay Analysis	*Packaging Tests*	
Private pharmacies and outlets	Convenience	104	39/104 (38%)†	31/84 (38%)	39/104 (38%)
Private pharmacies and outlets	Convenience and randomly‡	391	196/391 (50%)	195/391 (50%)	195/391 (50%)
Public and private pharmacies and outlets and facilities	Convenience	303	103/303 (34%); 99/103 (96)†	99/303 (33%)	99/303 (33%)
Public and private pharmacies, and outlets and facilities	Convenience	451	122/451 (27%); 30/122 (25%)†	72/111 (65%)	88/111 (79%)§
Private pharmacies and outlets	Stratified random sampling	30	27/30 (90%)	26/30 (87%)	27/30 (90%)
NS	Convenience	39	2/39 (5%)†	Not tested	2 (5%)
Private pharmacies and outlets	Systematic random sampling	119	8/119 (7%)	Not tested	NA
Private and public outlets	Convenience	92	57/92 (62%)	Not tested	NA
Private pharmacies only	Convenience sampling from various vendors	284	112/284 (39%)	Not tested	49/284 (18%)
Public and private outlets	Convenience	116	47/116 (41%)	Not tested	NA

continued

TABLE 3–7 *Continued*

	Location	Date of Sample Collection	Drug Tested	Method of Testing
Thoithi et al. (2008)	Kenya	2001–2005	Artemether, dihydroartemisinin, quinine, sulfadoxine-pyrimethamine, amodiaquine	Tests of uniformity of weight, content of active pharmaceutical ingredient, dissolution
Atemnkeng et al. (2007)	Kenya and Democratic Republic of Congo	2004	Artemether, arteether, artesunate, dihydroartemisinin	HPLC with European Pharmacopoeia standards
Tipke et al. (2008)	Burkina Faso	2006	Artesunate, artemether lumefantrine, quinine, chloroquine, sulfadoxine-pyrimethamine, amodiaquine	Packaging analysis, disintegration analysis, colorimetric tests, thin layer chromatography, ultraviolet-visible spectroscopy
U.S. Pharmacopeia (2009)	Madagascar, Senegal, Uganda	2008	Artermisinin-combination treatment, sulfadoxine-pyrimethamine	Compendial quality testing according to U.S. Pharmacopeia standards
WHO (2011)	Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania,	2008	Artermisinin-combination treatment, sulfadoxine-pyrimethamine	Compendial quality testing according to U.S. Pharmacopeia standards
Kibwage (2005)	Kenya	Not provided	Sulfadoxine-pyrimethamine	Dissolution analysis
Jande et al. (2006)	Tanzania	Not provided	Sulfadoxine-pyrimethamine	Dissolution analysis
Taylor et al. (2001)	Nigeria	Not provided	Quinine, choroquine, sulfadoxine-pyrimethamine, proguanil	HPLC with British Pharmacopoeia, dissolution analysis
Smine et al. (2002)	Senegal	Not provided	Choroquine, sulfadoxine-pyrimethamine	U.S. Pharmacopeia standards for active pharmaceutical ingredient testing
Minzi et al. (2003)	Tanzania	Not provided	Sulfadoxine-pyrimethamine, amodiaquine	HPLC, dissolution tests

Obtained From	Sampling Technique	Total Sample Tested	Samples That Failed Testing		Falsified*
			Chemical Assay Analysis	*Packaging Tests*	
Public and private outlets	Convenience	41	11/41 (27%)	Not tested	NA
Randomly, from both public and private pharmacies or outlets	Convenience sampling of different forms of drug	24	9/24 (38%)	Not tested	NA
Private and public pharmacies or outlets	Convenience	77	32/77 (42%); 1/32 (3%)†	28/77 (38%)	29/77 (38%)
Private and public pharmacies and outlets	Convenience	197	64/197 (32%)	Not tested	NA
Public and private outlets	Convenience	267	72/267 (27%)	Not tested	NA
Public and private outlets	Convenience	33	23/33 (69%)	Not tested	NA
Public and private outlets	Convenience	9	5/9 (55%)	Not tested	NA
Private and public pharmacies and outlets	Random	284	119/284 (42%)	Not tested	NA
Public and private outlets	Random	27	15/27 (56%)	Not tested	NA
Public and private outlets	Convenience	33	10/33 (30%)	Not tested	NA

continued

TABLE 3–7 *Continued*

	Location	Date of Sample Collection	Drug Tested	Method of Testing
Maponga et al. (2003)	Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	Not provided	Choroquine, sulfadoxine-pyrimethamine	HPLC, dissolution analysis, drug-specific assays
Gaudiano et al. (2007)	Angola, Burundi, Congo	Not provided	Quinine, choroquine, sulfadoxine-pyrimethamine, mefloquine	HPLC with U.S. Pharmacopeia standards, uniformity of mass, disintegration analysis
Aina et al. (2007)	Nigeria	Not provided	Choroquine tablets, syrups, and injections	British Pharmacopoeia dissolution tests, active pharmaceutical ingredient assay, disintegration tests
Kaur et al. (2008)	Tanzania	Not provided	Artemisnins, quinine, antifolates, sulfadoxine-pyrimethamine, amodiaquine	HPLC and dissolution analysis with U.S. Pharmacopeia standards
Bate et al. (2008)	Ghana, Kenya, Nigeria, Rwanda, Tanzania, Uganda	Not provided	Artesunate, artemether, dihydroartermisinin, artemether-lumefantrine, sulfadoxine-pyrimethamine, mefloquine, amodiaquine	Thin layer chromatography or dissolution analysis
Ofori-Kwakye et al. (2008)	Ghana	Not provided	Artesunate	Colorimetric tests, disintegration tests, European Union Pharmacopoeia standards
Onwujekwe et al. (2009)	Nigeria	Not provided	Artesunate, dihydroartemisinin, chloroquine, quinine, sulfadoxine-pyrimethamine	HPLC and dissolution analysis with U.S. Pharmacopeia standards

Obtained From	Sampling Technique	Total Sample Tested	Samples That Failed Testing		Falsified*
			Chemical Assay Analysis	*Packaging Tests*	
Private and public pharmacies and outlets	Convenience	278	5–100%¶	Not tested	NA
Mainly small, private pharmacies and outlets	Convenience	28	16/28 (57%); 1/16 (6%)†	Not tested	1/28 (4%)
Public outlet	Convenience	32	19/32 (59%)	Not tested	NA
Private and public pharmacies and outlets	Random	301	38/301 (12%)	Not tested	NA
Private pharmacies and outlets	Convenience	210	73/210 (35%)	Not tested	NA
Public and private outlets	Convenience	17	14/17 (82%)	Not tested	NA
Private and public pharmacies and outlets	Stratified random sampling	225	60/225 (27%)	Not tested	NA

continued

TABLE 3–7 *Continued*

	Location	Date of Sample Collection	Drug Tested	Method of Testing
Newton et al. (2011)	Burkina Faso, Chad, Cameroon, D.R. Congo, Ghana, Kenya, Nigeria, Rwanda, Senegal	2002–2010	Artesunate, dihydroartemisinin, dihydroartemisinin-piperaquine artemether-lumefantrine, artemether-amodiaquine, amodiaquine, halofantrine	HPLC, mass spectroscopy, pollen analysis, X-ray diffraction, packaging analysis

NOTE: DFID = Data are n/N (%), unless otherwise indicated. Samples failing chemical assay analysis might have failed packaging analysis; HPLC = high-perfomance liquid chromatography; NA = not applicable; NS = not specified.

* *Falsified* is used as a synonym for *counterfeit*.

† Samples with no active pharmaceutical ingredient.

Obtained From	Sampling Technique	Total Sample Tested	Samples That Failed Testing		
			Chemical Assay Analysis	*Packaging Tests*	Falsified*
Pharmaceutical companies, private and public pharmacies	Convenience	59	35/59 (59%); 11/35 (31%)*¶	26/36 (72%)	14/59 (24%)

‡ 115 samples from Laos were randomly selected.

§ Only tetracycline, quinine, and artesunate were tested.

¶ Varies substantially by drug and country; not included in analysis.

SOURCE: Nayyar et al., 2012. Reprinted from the *Lancet* with permission from Elsevier.

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4

Causes of Falsified and Substandard Drugs

The committee recognizes that the factors that encourage the proliferation of substandard and falsified medicines are different but overlapping. In general, neglect of good manufacturing practices, both accidental and deliberate, drives the circulation of substandard drugs, while falsification of medicines has its roots in crime and corruption. Both types of products circulate because of the erratic supply and constant demand for medicines and weaknesses in the regulatory system. An inaccurate or inadequate understanding of the problem among health workers and the public contributes to the problem.

REASONS FOR SUBSTANDARD DRUGS

As Chapter 1 explains, substandard drugs are those products that fail to meet the specifications set by the regulatory authority and delineated in a pharmacopeia or the manufacturer's dossier. Substandard medicines may, for example, be made in such a way that they do not dissolve properly; they may be of incorrect hardness or osmolarity; they may contain improper doses of the active ingredients; or be made from impure or unstable ingredients. Failure of good manufacturing practices is the root cause of substandard drugs.

Uneven Manufacturing Quality

Any company can make mistakes, but adherence to good manufacturing practices makes mistakes less likely and easier to correct. A factory

Key Findings and Conclusions

- There are equipment, staffing, and process costs necessary to meet international good manufacturing practices in the pharmaceutical industry.
- Lack of investment capital and poor infrastructure hold back some small- and medium-sized drug companies in developing countries from meeting international standards.
- For want of investment in pharmaceutical manufacturing, the poor pay more for substandard medicines.
- Unscrupulous manufacturers will deliberately produce poor-quality drugs, if the odds of getting away with it are favorable.
- When regulatory checks on production are inconsistent, procurement practices can help ensure that honest manufacturers get the largest market share.
- The World Health Organization's (WHO's) Model Quality Assurance System for procurement is a useful independent standard for procurement agencies.
- National and international procurement agencies should follow the WHO's guidelines for procurement. Small agencies should not procure directly from manufacturers.

run in accordance with best practices does not need to be the most technologically advanced or use state-of-the-art equipment, but there are costs to bring a factory up to standard, train staff on appropriate protocols, and observe them consistently. There are many exemplary manufacturers in developing countries that observe international best practices. There are also many that do not, but they operate anyway, either because the regulatory authority is unaware of the problem, or because regulators are under pressure to ignore it in the name of promoting industry.

Quality control is a part of good manufacturing practices sometimes neglected in developing countries. The WHO compendium on pharmaceutical manufacture describes the importance of having quality-control staff who are separate from production staff, working in an independent department (WHO, 2007b). A manager trained in quality control should supervise this department and run an equipped quality-control laboratory (WHO, 2007b). Quality-control staff should verify that everything that is a part of the factory's product, including packaging, starting materials, intermediates, and finished products, meets requirements (WHO, 2007b). They may also do internal inspections and quality audits and evaluate the quality controls used by their suppliers (WHO, 2007b). The majority of the pharmaceutical industry in the poorest countries only formulates and re-

packages finished medicines, also called secondary and tertiary production (see Box 4-1). Confirming the quality control measures used by suppliers, who are often in other countries, is particularly difficult for these firms.

Formulation companies have about a 6-month lag between placing an order for an active ingredient and selling a finished drug (Bumpas and Betsch, 2009). This delay can be even longer for firms in landlocked countries or places where customs clearance and transportation from the port of entry are slow or unpredictable (McCabe, 2009). It takes substantial working capital to cover costs during those lags (Bumpas and Betsch, 2009). Adding to the expense are the active ingredients themselves, which can cost thousands of dollars per kilogram; buying from WHO-prequalified or stringent-regulatory-authority–approved suppliers can add a 100 percent markup to the sale price (Bumpas and Betsch, 2009). The market for active ingredients has been especially volatile in recent years because of increasing costs of raw materials and growing environmental regulation in India and China (Bumpas and Betsch, 2009). Price volatility further complicates business for smaller firms, who tend to deal with less consistent (therefore cheaper) suppliers who are more vulnerable to market shocks. Although proper quality-control measures require purchasing only from suppliers who observe good manufacturing practices, supplier quality is often neglected because of logistical and financial obstacles. And, because the cost of active ingredients is by far the largest fraction of overall cost, a small reduction in active ingredient can vastly increase the profit margin.

Good quality comes at a price, either from equipment costs, better ingredients, or the higher process cost of quality assurance. The water filtration system is a high risk for microbial growth in any pharmaceutical plant and should be monitored vigilantly (WHO, 2007b). Microbial contamination is more of a threat in countries with poor water quality; much equipment cannot run on erratic power supplies (Anderson, 2010). Drug manufacturers also need an air handling system that will prevent dust and residue from one work area from contaminating other parts of the factory (WHO, 2007b). The adequacy of the air handling becomes more important in areas of the factory where different products are being processed at the same time and opportunities for cross-contamination abound (WHO, 2007b).

Some small-scale pharmaceutical companies make few finished formulations, but others make a wide range of products. Small firms are not generally able to dedicate equipment to specific products; equipment cleaning and cleaning validation become especially important. When equipment used for multiple products is not properly cleaned, and the cleaning not validated prior to changing the product line, the drugs produced can become contaminated. This type of contamination is difficult to detect. Quality-control assays generally test for the presence of the known ingredients, not the wide

BOX 4-1
The Medicines Manufacturing Process

Drugs are made with four or five main steps between the raw materials and the packaged final formulation (Figure 4-1). Medicines manufacture in the poorest countries is generally limited to the last steps in this process: formulation and packaging (Bumpas and Betsch, 2009; IFC, 2007). Of the 46 countries in sub-Saharan Africa, about 80 percent have local pharmaceutical industries, but only South Africa produces active ingredients (Bumpas and Betsch, 2009). South Africa alone accounts for 70 percent of the region's medicines production (Bumpas and Betsch, 2009).

The firms that make final formulations in developing countries buy excipients and active ingredient from chemical suppliers abroad, mostly from China and India. China supplies about 43 percent of the world's active ingredients for anti-infective medicines and exports 77 percent of the active ingredient made in the country, a $4.4 billion industry. India exports 75 percent of the $2 billion worth of active ingredients it produces (Bumpas and Betsch, 2009).

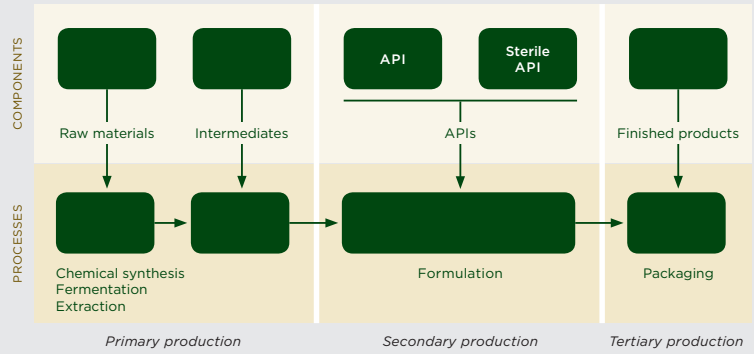

FIGURE 4–1 Schematic block diagram of a pharmaceutical manufacturing process.
NOTE: API = active pharmaceutical ingredient.
SOURCES: Adapted from Kaplan and Liang, 2005; Wilson et al., 2012.

range of possible unknown contaminants. Good pharmaceutical manufacturing requires drug producers to follow a cleaning protocol laid out in their standard operating procedures and to follow cleaning with validation testing (APIC, 1999; WHO, 2007b).

There is significant expense necessary for pharmaceutical companies to follow good manufacturing practices. Multinational companies, both

innovator and generic, operate on a scale that allows them to recover the costs of running high-quality factories. This is not true for many smaller manufacturers in developing countries. In India, for example, large pharmaceutical companies supply medicines and vaccines of the highest quality to every country in the world, but thousands of small manufacturers struggle to implement quality-assurance and quality-control procedures (Kaplan and Laing, 2005). A World Bank study found that one-tenth of Indian registered pharmacies report substandard medicines, most of them coming from small- and medium-sized producers (Kaplan and Laing, 2005). Because the registered pharmacy is the most strictly regulated medicines outlet in India, the proportion of substandard medicines sold in the informal market is presumably much higher. The problem is not limited to India. In a survey of antibiotic quality in Indonesia, investigators found 89 percent of samples of one local company's cotrimoxazole were substandard (Hadi et al., 2010).

Critics of local manufacture have cited these problems as reasons against pharmaceutical manufacturing in low- and middle-income countries (Ahmed, 2012; Bate, 2008). This may be a short-sighted argument. Domestic manufacture of medicines is an important part of health and industrial policy in many countries. Governments are understandably eager to ensure a safe drug supply for their population. In theory, locally made products could be cheaper because of lower shipping costs incorporated into the final price (Kaplan et al., 2012). Manufacturing medicines also gives people jobs and facilitates technology transfer (Wilson et al., 2012). Companies that start out packaging only finished drugs will slowly develop the trained workforce needed for more complicated secondary and primary manufacturing.

Initial capital investments and infrastructure problems stand between quality medicines and many small- and medium-sized medicine manufacturers. There are companies in developing countries that want to meet international quality standards and buy from reliable suppliers, but they fail to do so for reasons beyond their control. Governments alone cannot supply the technical depth or money to fix these problems (Wilson et al., 2012). The private sector must be involved. The International Finance Corporation (IFC) and the Overseas Private Investment Corporation (OPIC) can work to encourage private sector growth in developing countries. With the initial investments made, governments can take on the more manageable role of encouraging partnerships with foreign manufacturers.

Recommendation 4-1: The International Finance Corporation and the Overseas Private Investment Corporation should create separate investment vehicles for pharmaceutical manufacturers who want to upgrade to international standards. Governments can complement this effort by encouraging partnerships between local and foreign manufacturers.

Poor infrastructure, management problems, and insufficient training for staff can all hold back pharmaceutical manufacturers in low- and middle-income countries. While the extent to which each of these factors impedes progress varies among countries, there is a common problem of lack of capital (Cho et al., 2012; Patricof and Sunderland, 2005). Small- and medium-sized businesses have a particularly difficult time securing business improvement loans, as do firms in Africa (Patricof and Sunderland, 2005).

The only capital available to many small- and medium-sized drug manufacturers is the company's already meager profits. Reinvesting profits in capital improvements is not a quick or reliable path to develop a modern manufacturing infrastructure (UNDP, 2004). In developed countries small- and medium-sized firms might mortgage their assets to raise money, but mortgage laws and bank policies often disallow this in low- and middle-income countries (UNDP, 2004). The equipment and supplies needed to observe good manufacturing practices must be bought on foreign markets with hard currency, which banks in poor countries may only have at certain times of year (McCabe, 2009).

Manufacturers in developing countries often have to absorb their customer's debts, further reducing their working capital (McCabe, 2009). Therefore, small- and medium-sized companies are risky investments. Their national banks find the costs of the initial risk assessment both too costly and too complicated to make loans attractive (UNDP, 2004). Barriers to accessing capital hold back small- and medium-sized businesses, the "engines of job creation," in the parts of the world most desperate for more and better jobs (*Economist*, 2012b; UNDP, 2004, p. 4). When these enterprises are drug companies, there is an added drawback. For want of investment capital, the poor pay higher prices for substandard drugs (UNDP, 2004).

The IFC and OPIC

The IFC and OPIC both promote private-sector development as a means to reduce poverty. The IFC's goals include promoting open markets and jobs that deliver essential services in developing countries (IFC, 2012c). To this end, it provides investment services to help promote private-sector growth in developing countries. Through investments, advisory services, and asset management, the IFC aims to reduce poverty and encourage economic growth (IFC, 2012d). The IFC works with the World Bank Group, but with financial and legal autonomy. Its membership is made up of 184 developed and developing countries (IFC, 2012f).

The IFC accepts applications for ventures in member countries, often when a company cannot access the requisite capital in its home country (IFC, 2012a,d). The organization serves a wide range of industries, including health, education, infrastructure, agribusiness, and manufacturing (IFC, 2012b).

There is precedent for the IFC working with pharmaceutical companies in developing countries (IFC, 2012e). Alongside investment in upgrading pharmaceutical standards, its membership structure could be used to set up partnerships between pharmaceutical companies in developing countries and those in countries with strict regulatory authorities. The IFC does not lend directly to small- and medium-sized enterprises but can invest in organizations that will in turn lend to smaller companies (IFC, 2012a).

OPIC, the U.S. government's development finance agency, does make loans to small businesses (OPIC, 2012a). Its loans and guaranties for small- and medium-sized business financing range from $350,000 to $250 million (OPIC, 2012a). OPIC often finances capital costs such as equipment and construction (OPIC, 2012a). It also funds national lenders to expand their lending capacity to small- and medium-sized enterprises (OPIC, 2012a). Although the agency does not grant requests that are solely for acquisitions or working capital, it will support the expenses if they are part of a larger project (OPIC, 2012a).

OPIC creates ways for investing in developing countries, to the benefit of both development abroad and private firms in the United States (OPIC, 2012a). OPIC's investment policies promote sustainable development and human rights; investment in medicines manufacture is well aligned with these priorities (OPIC, 2012b).

Investment in upgrading pharmaceutical manufacturing standards advances the goals of both organizations; there is also precedent for such investments. In August 2012, the IFC invested $47 million in Fosun Pharma, a leading Chinese drug company that makes, among other products, antimalarials for aid organizations (Yu and Hindenburg, 2012). OPIC supported the development of generic drug manufacturing in Afghanistan in 2005 (OPIC, 2006). The committee commends these projects and encourages OPIC and the IFC to make more similar investments in a wider range of companies.

Investment in pharmaceutical manufacturers in low- and middle-income countries has immediate benefits to the manufacturers trying to upgrade their production. There are also spillover benefits to a cohort of workers trained in good manufacturing practices and the use of modern equipment. These workers may eventually find new positions in other industries, sharing their knowledge about manufacturing, and contributing to a more competent workforce. IFC and OPIC investment will help buyers identify manufacturers who are serious about running a responsible business and willing to make expensive changes to their methods. Firms that make these investments are clearly trying to eliminate substandard production. Building responsible firms gives procurement agencies that are forced to buy locally produced medicines a high-quality alternative to the status quo.

Governments in low- and middle-income countries can complement investments in the private sector by encouraging partnerships between for-

eign and local manufacturers who upgrade their production. Partnerships can continue the cross-fertilization of ideas that direct investment sparks. Manufacturing staff in developing countries who work with their counterparts abroad learn about regulatory science and business management, for example. This exposure benefits all parties and advances an international network of high-quality drug manufacturers.

Tiered Production

In practice it is difficult to distinguish the quality failures that are to blame on a manufacturer's inability to meet international best practices from those which come from a decision to cut corners and produce inferior products for poorly regulated markets. When a producer capable of meeting international standards fails to do so consistently and only in product lines sold to the poor, one may conclude that the noncompliance is part of a more insidious system.

Rich countries enforce high quality standards for medicines, and manufacturers recognize the need to use good-quality ingredients and good manufacturing practices to sell in these markets. United Nations (UN) agencies and the larger international aid organizations will also refuse to do business with companies that cannot meet stringent regulatory authority quality standards. Manufacturers are aware, however, that low- and middle-income countries are less likely to enforce these standards. Some companies exploit this and produce drugs of lower quality for the loosely regulated markets (Caudron et al., 2008). When a manufacturer produces medicines of inferior quality for less exacting markets, it is known as tiered or parallel production (Caudron et al., 2008; World Bank, 2007).

Tiered production is a complicated problem, in part because some kinds of tiered production are legal. International manufacturers may supply to multiple markets which use different legal product quality standards. For example, the British Pharmacopoeia monograph for amoxicillin gives no dissolution standard (British Pharmacopoeia, 2012); the U.S. Pharmacopeia does (USP-NF, 2010). Assay limits may also be different, making a product illegal by one pharmacopeia but legal by another. A manufacturer may supply to one country that stipulates a uniformity of dosage at 90-120 percent of declared dosage and to another country that stipulates 85-115 percent, for example. Both these standards aim to correct for the fact that drugs such as antibiotics degrade quickly, making a high initial dose acceptable. However, manufacturers could technically aim to fill only the lower bound of the dosage requirements and be within the letter of the law. A study of amoxicillin samples in Arab countries found that most samples' active ingredient concentrations were bordering the U.S. Pharmacopeia lower limit (Kyriacos et al., 2008). The authors admitted, however, that many of

the problematic samples would have been judged acceptable by the wider British Pharmacopoeia standard (Kyriacos et al., 2008).

Participants at the public meetings for this study mentioned concerns with parallel production, but evidence for it is largely anecdotal. There is reason to suspect tiered manufacturing when the dose of active ingredient is consistently lower, never higher, than the label claim (Bate et al., 2009b). Drugs, especially tablets, of less than half the labeled potency before the expiry date are particularly dubious. In a hospital dispensary in rural Nepal, a bottle of pediatric amoxicillin from a WHO-certified producer with many obvious labeling and packaging defects also suggests either parallel manufacturing or diversion, a problem discussed in Chapter 5 (Brhlikova et al., 2007).

Tiered manufacturing is a rising problem in emerging manufacturing nations. A 2006 *Lancet* report described a shift in Russia from most bad medicines being falsified drugs made "in basements and small backroom enterprises" to ones coming from legitimate companies running "a 'night shift' to produce extra quantities of a certified drug that does not pass quality control, or sophisticated copies of well-known drugs . . . often with reduced levels of expensive active ingredients" (Parfitt, 2006, p. 1481). The United Nations Office on Drugs and Crime (UNODC) described a similar case in India. The U.S. Food and Drug Administration (FDA) revoked market authorization from an Indian drug manufacturer found to be producing antibiotics with no active ingredients (UNODC, 2010). After losing its license, "the factory continued to operate at night, until an evening raid by police uncovered an underground cellar in the factory, where exact look-alikes of several popular, fast-moving, high-cost medicines were being manufactured, most of which contained no active ingredient" (UNODC, 2010, p. 187).

Jiben Roy reported on a similar case: A Bangladeshi company deliberately kept the active ingredients in paracetemol, ampicillin, and cotrimoxazole below the labeled concentrations after repeated warnings from the regulatory authority (Roy, 1994). In the same paper he attributed the manufacturer's quality failures in their cheaper product lines to negligence alone. Their B-vitamins, for example, contained the proper ingredients, but in erratic doses (Roy, 1994). This paper was able to make distinctions between the deliberate quality failures and negligence because the author had close knowledge of the manufacturer and its history. Usually only the national regulatory authority could have the information needed to make this distinction. In many countries, even the regulatory authority would not have that information or the political will to act on it (Christian et al., 2012b).

Pinpointing cases of deliberate tiered manufacturing is difficult to do, though it is easier to see practices that allow it happen. Poor oversight of

contract manufacturers is one such practice. A combination of technological sophistication and low labor costs in some developing countries attract drug companies, both innovator and generic, to contract with manufacturers abroad (PWC, 2010). Setting up a drug factory in India, for example, costs companies about 40 percent of what they would pay in North America or Europe (PWC, 2010).

Companies provide contract manufacturers with the materials, including packaging, to make their products. As Dilip Shah, Secretary General of the Indian Pharmaceutical Alliance, explained to a committee delegation in India, "Very few companies, foreign or domestic, monitor the [contract manufacturer's] process loss of raw materials, active ingredients, and packaging materials. I have known of cases of 15 to 20 percent packaging material losses and companies are not bothered." These contract manufacturers have established distribution channels; it is not difficult for them to introduce falsified drugs into the market. Because the contract manufacturers have the processes and materials needed to produce a proper drug, they will sometimes sell perfectly made drugs outside of the licit distribution system. More often, they will use legitimate packaging to disguise a false product.

Pharmaceutical exporting countries can also unintentionally facilitate tiered manufacturing by not requiring the same evaluations for exported drugs as for those sold domestically (Caudron et al., 2008). In general, regulatory agencies are responsible for protecting their country's domestic medicine supply; ensuring quality for exported products is often beyond their mandate and budget. Importing countries' regulatory agencies have the right to inspect producers abroad, but the breadth of international supply chains makes this a difficult job even for the most mature agencies (IOM, 2012). It is more difficult for low- and middle-income countries to ensure checks on drug quality during manufacture, a problem discussed later in this chapter.

Procurement and Substandard Medicines

When regulatory checks on production are inconsistent, procurement practices can help ensure that quality medicines get the largest market share. The Global Fund explains the goal of good procurement as supplying medicine "meeting agreed quality standards at the lowest possible price and in accordance with national and international laws" (Global Fund, 2009, p. 6). Government agencies procuring medicines have to reconcile a tension between quality and price (Torstensson and Pugatch, 2012). The WHO *Operational Principles for Good Pharmaceutical Procurement* discusses the hidden costs of cheap drugs, including poor shelf life and health threats (WHO, 1999, 2002a). The firms that offer the cheapest prices may do so by buying impure ingredients or cutting corners in formulation.

Good procurement dictates that the cheapest tenders are not accepted

if they are of dubious quality, but it is difficult not to be swayed by price, especially for provincial health offices and other small procurement agencies (Bate, 2007; Harper et al., 2007). Chinese provincial procurement, for example, is known for "pressuring manufacturers to produce the lowest cost possible while preserving their profits" (Burkitt, 2012). These agencies face pressure to supply medicines for entire populations on tight budgets; sometimes there is added demand to support local manufacturers (Dickens, 2011; Torstensson and Pugatch, 2012). Openness in procurement can balance these pressures by exposing unnecessarily high costs or bad quality, but transparency, which also includes vetting procurement officers for conflicts of interest, auditing suppliers, documenting decisions, and scrutinizing procurement agents, adds costs to the process (Torstensson and Pugatch, 2012). For these reasons the Organisation for Economic Co-operation and Development (OECD) recommends "an adequate degree of transparency in the entire procurement cycle to promote fair and equitable treatment for potential suppliers" (OECD, 2009, p. 11).

Over the longer term, more openness is a good investment. In Argentina, for example, a health transparency program brought down the procurement costs of medicines (Lewis, 2006). Reducing costs of procurement would be especially helpful in the poorest countries, which tend to spend a higher proportion of their health budget on drugs and where medicines are often expensive (Torstensson and Pugatch, 2012). In a study of 36 low- and middle-income countries, Cameron and colleagues found that public procurement agencies in the western Pacific, Africa, and the former Soviet bloc pay an average of 34 to 44 percent above the international reference prices (Cameron et al., 2008).

Donors may attempt to cover unmet demand for drugs, though donor procurement also has problems. Methods for assuring the quality of donated medicines vary by donor. The United States Agency for International Development (USAID) requires FDA, or other stringent regulatory agency, approval on donated medicines. It also has a prequalification process to vet the wholesalers it works with (GAO, 2012). USAID contractors are often responsible for implementing these rules in the field (Moore et al., 2012). The Global Fund will accept WHO prequalification, the approval of stringent regulatory authorities, or the review of an expert panel, especially for finished pharmaceuticals that are not prequalified by the WHO (GAO, 2012). Many European donors ask their recipients to assure quality of medicines procured with donated funds (Moore et al., 2012). Table 4-1 gives an overview of different agencies' quality assurance policies.

Proper precaution in the medicines procurement process can prevent poor-quality products from infiltrating the market. Good procurement involves separating the various steps of procurement process identified in Table 4-2. Good procurement also puts a strong emphasis on controlling corruption and promoting transparency. The WHO's Model Quality Assur-

ance System for procurement lays out the steps necessary for efficient and open procurement of the best-quality medicines possible (WHO, 2007a).

Recommendation 4-2: Procurement agencies should develop a plan, within the next 3 to 5 years, to comply with the World Health Organization's Model Quality Assurance System for procurement agencies and work to remove any barriers to compliance.

The technical aspects of good pharmaceutical procurement and distribution practices have always been part of training courses on medicine supply management (MSH, 2012). The most complete and modern procurement guideline is the 2006 *Model Quality Assurance System for Procurement Agencies*, a United Nations interagency document endorsed by the WHO, Unicef (the United Nations Children's Fund), the UN Development Program and Population Fund, and the World Bank (WHO, 2007a). The model draws on the accumulated experience of these agencies' procurement experts and combines advice on the procurement of medicines, vaccines, diagnostic kits, and devices. The model focuses on four key activities: prequalification of pharmaceutical products and manufacturers and drug purchase, storage, and distribution. It presents the recommended practices in great detail (WHO, 2007a).

At its launch in 2006, the model had an aspirational element; it described standards that few if any of the international procurement agencies were able to maintain at that time. In the past 6 years, large procurement agencies have made great progress toward meeting the standards laid out in the model (van Zyl et al., 2012). The committee sees the model quality assurance system as a useful independent standard to assess procurement agencies. The system is a practical tool that can be used by national and international procurement agencies. Eventually, agencies can use the WHO tool to prequalify suppliers; prequalification is a recommended piece of a procurement system (MSH, 2011).

Modern pharmaceutical chains are international. No country is self-sufficient in its medicine supply. Pharmaceutical procurement almost always means working with foreign suppliers; a practice that exceeds capacity of national regulators, who cannot hope to inspect foreign manufacturers as they would domestic ones. Good procurement also means that only organizations that follow the model system should import medicines. Small-scale importation and procurement by small actors threaten the medicines supply chain. This risk is not only present in developing countries. In many OECD countries, pharmacies and private clinics import drugs directly from suppliers, greatly increasing the risks of introducing a poor-quality product to the market.

TABLE 4–1 Overview of Selected Donors', Procurement Service Agencies', and Quality-Assurance Organizations' Quality-Assurance Policies

Organization	Policy	Standards	Assessment Tool
WHO	Stringent regulatory authority approval; WHO prequalification; or expert review panel recommendation	WHO Good Manufacturing Practices (GMP) and WHO Model Quality Assurance System (MQAS) for procurement agencies	Dossier reviews and site inspections; recognition of approval by stringent regulatory agencies (FDA, EMA, etc.)
Global Fund	WHO prequalification; stringent regulatory authority approval; or expert review panel recommendation (Daviaud and Saleh, 2010)	WHO GMP and WHO MQAS (Global Fund, 2012)	Expert review panel dossier reviews and inspections (Daviaud and Saleh, 2010)
European Commission's Humanitarian Aid Department (ECHO)	Quality-assurance guidelines are based on WHO prequalification and model quality assurance system	"Every activity in the procurement process should be carried out according the WHO standards and norms relating [to] the quality assurance of pharmaceutical products which include good manufacturing practices; good distribution practices; good storage practices; good procurement practices based on WHO's Model Quality Assurance System for procurement agencies" (European Commission, 2011, p. 46).	None
World Bank	Prequalification of bidders (not products)	WHO GMP	Audits and inspections

continued

TABLE 4-1 *Continued*

Organization	Policy	Standards	Assessment Tool
USAID	FDA or other stringent regulatory approval; WHO manufacturer and product prequalification; and Supply Chain Management System procurement agency prequalification	WHO GMP; WHO MQAS; U.S. Pharmacopeia; and International Pharmacopoeia	Dossier reviews and inspections and product quality assessments
Department for International Development (DFID)	Procurement of commodities are done through third parties such as multilateral organizations, partnerships, or procurement agencies. DFID relies on the quality-assurance policies of those third parties (personal communication, James Droop, DFID, October 17, 2012).	Stringent regulatory approval; national drug regulatory authority approval; WHO prequalification; and expert review panel approval (DFID, 2012)	Third-party compliance is monitored through normal channels of oversight such as boards, steering committees and program reviews (personal communication, James Droop, DFID, October 17, 2012).
The Bill & Melinda Gates Foundation	WHO prequalification of grantees and partners (personal communication, Vincent Ahonkhai, The Bill & Melinda Gates Foundation, October 3, 2012).	Grantees and partners use WHO GMP and the WHO MQAS (personal communication, Vincent Ahonkhai, The Bill & Melinda Gates Foundation, October 3, 2012).	Funds WHO to conduct dossier reviews and required inspections through its prequalification process. The foundation also reviews grantee and partner prequalification performance reports provided by WHO (personal communication, Vincent Ahonkhai, The Bill & Melinda Gates Foundation, October 3, 2012).
Clinton Health Access Initiative (CHAI)	Stringent regulatory approval of product dossiers and good manufacturing approval for manufacturing sites (personal communication, Kelly Catlin, CHAI, October 3, 2012).	Stringent regulatory authority approval and participation in the Pharmaceutical Inspection Cooperation Scheme (personal communication, Kelly Catlin, CHAI, October 3, 2012).	Independent evaluations of product dossiers (personal communication, Kelly Catlin, CHAI, October 3, 2012).

Organization	Policy	Standards	Assessment Tool
UNITAID, UNAIDS, and UNICEF	Stringent regulatory authority approval; WHO prequalification; expert review panel recommendation; and WHO/PAHO pooled procurement (Unicef, 2011)	WHO GMP; WHO MQAS (Unicef, 2011)	Dossier reviews and inspections
Doctors Without Borders (MSF)	MSF Qualification Scheme, WHO prequalification and stringent regulatory authority approval (MSF, 2006)	WHO GMP; WHO International Pharmacopoeia; European Pharmacopoeia; British Pharmacopoeia; U.S. Pharmacopeia; and MSF specifications for pharmaceutical products (MSF, 2006)	Product dossier and manufacturing site audits (MSF, 2006)

NOTE: DFID = Department for International Development; ECHO = European Commission's Humanitarian Aid Department; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; GMP = Good Manufacturing Practice; MQAS = Model Quality Assurance System for procurement agencies; PAHO = Pan American Health Organization; UNAIDS = Joint United Nations Programme on HIV/AIDS; Unicef = United Nations Children's Fund; USAID = United States Agency for International Development; WHO = World Health Organization.

SOURCE: Adapted from Moore et al., 2012.

Applying the Model Quality Assurance System to Secondary Procurement

The requirements for infrastructure, policies and documentation, prequalification, purchasing, receipt, and distribution of medicines laid out in the model quality assurance system are written for large national or international agencies (WHO, 2006a). Much of the most problematic procurement happens at subordinate levels, however. District hospitals and health posts in poor countries will not likely meet the model standards for premises, equipment, or staffing any time in the near future (Dickens, 2011).

In the meantime, if full preselection of quality suppliers is not possible, interim solutions such as a two-envelope system can help reduce bias toward the cheapest firms. In this system, used by the Delhi hospital system, bidders submit their technical statement of work and their costs in separate, sealed envelopes (Chaudhury et al., 2005). The reviewers evaluate the quality controls in the statement of work. Only if the quality controls are sufficient do they open the second envelope, containing the project budget.

Ultimately, medicine procurement is complicated and requires considerable investment in staff and procedures. While the WHO model system should guide drug procurement at the national level, small agencies will never command the economies of scale necessary for good and open procurement (Dickens, 2011; Rao et al., 2006; WHO, 1998). Cutting corners in procurement creates opportunities for substandard products to infiltrate the supply chain. Therefore, smaller organizations such as district health offices should be free to choose the products and amounts they need from licensed, national wholesalers or importers, but they should not procure directly from manufacturers.

The committee recognizes that licensing wholesalers and importers requires political will. It might take time to build momentum for this step, as discussed further in Chapter 5. Therefore, the committee recommends that national and international procurement agencies take 3 to 5 years to develop and implement their compliance plans. These plans will identify those agencies with the technical depth and buying power necessary to comply with the WHO system. These agencies can develop their quality-assurance system within the next 5 years. The regulatory authority can then license national procurement agencies to buy medicines directly from manufacturers. Agencies that are not able to comply with the WHO's minimum standards will not be licensed for procurement. Instead, these organizations will be able to order their medicines from licensed procurement agencies, thereby making more efficient use of their staff and budgets and avoiding the dangers of primary procurement.

TABLE 4–2 Pharmaceutical Procurement Best Practices

Pre-Procurement Stage
Ensure an adequate procurement infrastructure is in place.
Ensure health professional and technical capacity is high among officials.
Use written quality manual and written standard operating procedures.
Use of prescreening and prequalification is recommended for procurement agencies with limited capabilities.
Prequalification must include quality assurance and quality testing through product and manufacture assessments, including testing of batches.
Have management information systems in place to monitor actual supply and payment of drugs as well as post-supply quality.
Estimates of medicines needed should be based on data like past use, morbidity records, and consumption predictions.
Separate duties of pre-procurement process.
Procurement Stage
Procurement should be transparent, following formal written procedures and clear public selection criteria.
International competitive bidding ensures economy efficiency and transparency and should be used.
Separate duties of selection, product specification, and adjudication.
Quality assessment of drugs upon receipt, including lab testing, inspection of shipments, and certificate of analysis of delivered products.
Domestic preferencing should not compromise quality standards.
Ensure technical specifications are right (e.g., dosage, storage, shelf life, delivery expectations, etc.) in bidding documents.
Post-Procurement Stage
Continue to monitor quality of received drugs through independent testing.
Establish pharmacovigilance and adverse event reporting.
Conduct independent and transparent audits of procurement and supplier performance.
Regular new tenders should open to new bidders.

SOURCE: Adapted from Torstensson and Pugatch, 2012.

REASONS FOR FALSIFIED DRUGS

As Chapter 1 explains, the drug regulator, having the authority to license manufacturers and register medicines, can act against products made by known manufacturers. When the manufacturer is falsely represented

Key Findings and Conclusions

- Making fake medicine is an opportunistic crime, more common in places where regulatory oversight is weak or inconsistent.
- Corruption allows for the manufacture, trade, and distribution of falsified medicines. Complicit government officials are often bribed with revenue from the illicit pharmaceutical business.
- Criminals may intentionally price falsified products slightly lower than legitimate drugs in order to guarantee their market share but avoid consumer suspicion.
- Major pharmaceutical companies have security departments that work with regulators and law enforcement agencies. These departments gather 80 percent of the evidence for criminal prosecution.
- Law enforcement agencies are cracking down on pharmaceutical crime. Seizures of falsified medicine have tripled in Brazil and led to 1,900 arrests in China.

this is not possible. The regulator can only confirm that the producer is unknown and turn the case over to law enforcement. The police and detectives who inherit these cases have a difficult job gathering sufficient evidence for a prosecution; there is usually little if anything to tie the falsified drug in the market to the culprit (see Box 4-2). It is also hard to convince agents to investigate pharmaceutical crime when they are under immediate pressure to prosecute murders and other violent felonies. For all these reasons, falsifying medicines has been called the perfect crime (Dobert, 2012; Kontnik, 2004; Nelson et al., 2006).

Corruption and Organized Crime

Making fake medicine is not difficult. The least sophisticated operations manage with empty capsules bought in the open market or a handheld pill press and any powder to load into it. Production costs on fake drugs are low (Clark, 2008; Perrone, 2012). And, because the licit and illicit supply chains mix in unregulated markets (described in Chapter 5), the odds of getting away with the crime are good. As Chapter 3 describes, the global burden of falsified and substandard medicines is borne disproportionately by low- and middle-income countries. There is wide evidence that criminals frequently target inexpensive anti-infective medicines, mostly because they are bought often and by the largest segment of the population. The UNODC therefore describes making falsified medicines as an "oppor-

BOX 4-2
Fatal Falsified Iron

When a drug that had been on the market for 40 years killed a young, generally healthy woman in 2004 despite her six previous doses with no side effects, the technical director of the AstraZeneca subsidiary in Río Negra, Argentina, was alarmed and suspected impropriety. The drug was Yectafer, an injectable iron supplement given to the patient for her anemia. She died of liver failure within weeks of receiving the fatal injection, unable to undergo transplant surgery quickly enough to save her life (Loewy, 2007). A sample of the drug was sent for testing at the plant and was immediately identified as a fake: the package labels were applied incorrectly, the name of the drug written in a different font, and the color of the liquid significantly altered. Chemical analysis confirmed that the bottle did not contain iron sorbitol, the active ingredient in Yectafer, but a different form of iron at three times the stated dosage (Loewy, 2007). Despite an attempted recall, one more woman died in the ensuing months, and at least eight women undergoing the same treatment were hospitalized for liver damage, including a 22-year-old pregnant woman whose condition caused her to deliver her baby prematurely at 26 weeks (Loewy, 2007; WHO, 2006b).

Although some of the people involved in distributing the dangerous fake were charged for their crimes, lack of an effective paper trail prevented Argentine authorities from tracking down the manufacturer. The victims' youth lent an emotional appeal to this incident, making it the public face of drug regulation agenda, but Argentina was no stranger to tragedy of this sort. Fake drugs for treating Parkinson's disease circulated in 1997 and exacerbated the symptoms they were taken to prevent (Loewy, 2007). Weak regulation and the legal confusion made Argentina's drug supply vulnerable and hampered efforts to prosecute those involved (WHO, 2006b).

tunistic crime, emerging where regulatory capacity is low, not where profits would be highest" (UNODC, 2010, p. vi).

This is not to say that profits generated from falsifying drugs are insignificant. In a study of fake malaria medications in Southeast Asia, Dondrop and colleagues found the falsified artesenuate to be cheaper, but only somewhat, than the authentic one (Dondorp et al., 2004). By pricing their product just slightly under the legitimate drug, criminals can guarantee market share, but they avoid pricing it so low as to arouse suspicion. Falsified medicines can be priced less cautiously in the wholesale market, however, because these markets are less regulated and customers are not the general public but buyers for retail who are sometimes complicit. *Tempo*, an Indonesian news magazine, reported on "astonishingly low" prices

in a medicines wholesale market in Jakarta (Silverman et al., 1992). The story described how pharmacists unwilling to buy from the illegal markets probably could not survive in business (Silverman et al., 1992). Box 4-3 describes the profit motive of one American pharmacist dealing in diluted cancer drugs.

Interpol uses the term pharmaceutical crime to describe "the manufacture, trade and distribution of fake, stolen or illicit medicines and medical

BOX 4-3
Adulterated Cancer Drugs

Robert Courtney, a pharmacist in Kansas City, Missouri, made millions selling adulterated drugs to patients and physicians throughout the 1990s until 2001, when he was prosecuted for his crimes. Most famous for diluting chemotherapy drugs such as Taxol, Gemzar, Paraplatin, and Platinol, Courtney regularly sold tampered versions of 72 different prescription drugs. His first foray into pharmaceutical crime was illegally purchasing drugs at low cost and selling them at market value, as well as disguising generic drugs as their name-brand counterparts and charging the associated higher price. Seeking higher profits, he left the gray market and turned to dilution (Belluck, 2001; Draper, 2003).

Traditionally, oncologists purchase chemotherapy drugs and dissolve them in saline at their offices. Robert Courtney was one of the first pharmacists in the area to begin selling convenient, premixed cancer drugs. By adding extra saline he stretched out his drug supply and made enormous profit selling the expensive therapies. The practice was so lucrative that he began diluting more extensively, going so far that during the investigation it was found that all of the mixtures sampled contained 39 percent or less of the proper dose and one even contained less than 1 percent. The substantial profit margin on the diluted drugs was the motivating factor; in one case he allegedly made more than $700 from one prescription. Courtney has admitted that his actions were "out of greed" (Belluck, 2001).

Communication between Eli Lilly Corporation, which manufactures Gemzar, and a physician prescribing the drug brought the scandal to light. A sales representative noticed the discrepancy in the amount of Gemzar that Courtney was buying from them and the amount he was selling, which led to an investigation by the company (Belluck, 2001). Although Eli Lilly dropped the investigation when it found no evidence of Courtney's buying drugs elsewhere, the representative mentioned the finding to an affected physician, who sent samples of some of the drugs for testing. When the samples contained approximately one-third of the stated amount, she alerted authorities. After more than a decade of selling poor-quality drugs to more than 4,000 patients, Robert Courtney was investigated by the Federal Bureau of Investigation and the FDA for his crimes and sent to federal prison (Draper, 2003).

A medicines seizure in Shagamu, Nigeria, 2007.

SOURCE: © 2007 Opara Adolphus, Courtesy of Photoshare.

devices" (Interpol, 2012b). Pharmaceutical crime includes theft, trade, and the money laundering criminals use to cover their tracks (Interpol, 2012b). Corruption allows the crime to continue. Complicit government officials are often bribed with revenue from the underground pharmaceutical business (UNODC, 2010); criminal executives may be embedded in the government hierarchy (Parfitt, 2006). Threats and bribery are the purview of members of organized crime, who are often responsible for trafficking falsified medicines, perhaps attracted by the mild punishments discussed below (Beken and Balcaen, 2006; Interpol, 2012a). Interpol has evidence linking the trade in falsified drugs to Al-Qaeda and transnational crime syndicates (Beken and Balcaen, 2006; Liberman, 2012).

Enforcement and Punishment

When falsified medicines are also counterfeits that infringe on the trademarks of multinational pharmaceutical companies, the company targeted tries to respond. Major pharmaceutical firms have designated security departments that work with regulators and law enforcement to gather evidence for criminal prosecution (Cockburn et al., 2005). In general these companies collect evidence and build 80 percent of the case against the

criminals, then hand the investigation over to law enforcement (*Economist*, 2012a).

Law enforcement agencies, for their part, are cracking down more on pharmaceutical crime. The Chinese government, perhaps driven to improve China's reputation as the world leader in fake drugs, arrested more than 1,900 suspects from about 1,100 manufacturers in late July 2012 (Burkitt, 2012; Palmer, 2012; Quingyun, 2012). The 18,000 police officers working in simultaneous raids across the country seized a range of falsified products, including saline labeled as rabies vaccine and an obesity drug recalled from the Chinese market because of toxic side effects (Quingyun, 2012). It was not clear what products were destined for the domestic market and which were meant for export (Palmer, 2012).

In an analysis of the Brazilian federal police reports, Ames and Souza found that police seizure of falsified medicines roughly tripled between 2007 and 2010 (Ames and Souza, 2012). Most falsified products entered Brazil from Paraguay, and the arrests were made at the border (Ames and Souza, 2012). Some data suggest that arrests at the point of sale, manufacture, and distribution are more common, however (see Table 4-3). Box 4-4 presents the Pharmaceutical Security Institute's (PSI's) 2010 and 2011 data on arrests for pharmaceutical crime.

PSI data indicate that China and Brazil took the most police action

TABLE 4–3 Top Countries for Arrests, 2011

	Country	POS	Trans	Dist	Mfg	Theft	Unk	Total
1	China	74	3	92	120	0	110	**399**
2	Brazil	36	74	50	2	1	0	**163**
3	United States	47	1	62	0	1	1	**112**
4	Colombia	4	10	30	7	0	3	**54**
4	India	22	1	3	28	0	0	**54**
6	Pakistan	3	0	1	47	0	0	**51**
7	Thailand	37	0	3	10	0	0	**50**
8	South Korea	42	1	1	4	0	0	**48**
9	Israel	19	4	0	0	0	20	**43**
10	Poland	3	1	16	0	0	17	**37**
11	Spain	0	0	27	0	0	0	**27**

NOTES: Dist = distributing; Mfg = manufacturing; POS = point of sale; Trans = transporting; Unk = unknown.
SOURCE: PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012.

BOX 4-4
Pharmaceutical Security Institute Crime and Arrest Data

The Pharmaceutical Security Institute, a nonprofit network of 25 major pharmaceutical companies' security departments, maintains a database on compromised medicines (PSI-Inc., 2012c). In PSI records, every report of a fake product, either from member companies or from public sources, is an incident. Incidents vary in their size and time frame (PSI-Inc., 2012a). PSI also keeps records on arrests, gathered from members, law enforcement officers, and open sources. These data indicate 1,311 arrests for pharmaceutical crime in 2011, a 14 percent increase from their 2010 records (PSI-Inc., 2012b). For 44 percent of their 2011 arrests data and 59 percent of 2010 arrests data, PSI has sufficient information to tie an arrest to an incident report in their database (PSI-Inc., 2011).

In both 2010 and 2011, about one-quarter of incidents ended in an arrest. In 2011 PSI identified an increase in arrests at the point of sale and during distribution (PSI-Inc., 2011). Figure 4-2 compares PSI data from 2011 and 2010, excluding 191 incidents for which PSI had insufficient information to confidently identify the point on the supply chain where the arrest was made.

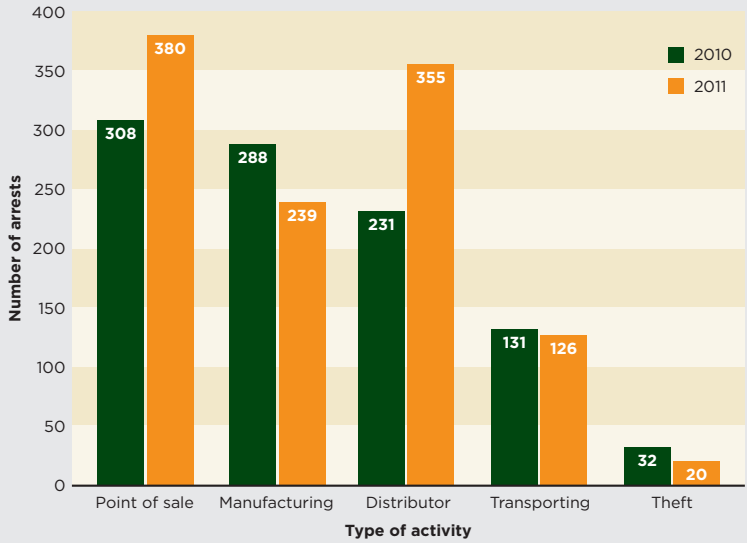

FIGURE 4-2 Arrests by activity, 2010–2011.
SOURCE: PSI-Inc., 2011.

TABLE 4–4 Top 10 Countries Ranked by Number of Counterfeit Drug Seizures and Discoveries in 2006

	Country	Number of Seizures
1	**Russia**	93
2	**China**	87
3	**South Korea**	66
4	**Peru**	54
5	**Colombia**	50
6	**United States**	42
7	**United Kingdom**	39
8	**Ukraine**	28
9	**Germany**	25
10	**Israel**	25

NOTE: PSI uses the term *counterfeit* broadly, the way this report uses the word *falsified*. See page 23.

SOURCE: PSI-Inc., 2006.

against falsified medicines in 2011. Table 4-3 presents the number of arrests in the PSI incident database by country. The countries with the most serious problems might have no arrests in a year, as arrests depend on government motivation to marshal the police. The momentum for labor-intensive police raids is difficult to sustain. Only half of the countries on PSI's 2006 arrests list appear on the same list in 2011 (see Table 4-4). In 2006 Russia led in arrests for pharmaceutical crime after a series of raids reported in the *Lancet* (Parfitt, 2006). At the time, Gennady Shirshov, director of a Russian pharmaceutical industry association, predicted that other criminal manufacturers would quickly replace the closed ones (Parfitt, 2006). Mr. Shirshov mentioned insufficient law enforcement interest in the problem but concluded, "The legislation is inadequate. It's a civil liability, not a criminal one . . . and the fines are negligible" (Parfitt, 2006, p. 2).

As Box 4-5 mentions, perpetrators who are caught falsifying medicine are punished leniently in some countries (Kyriacos et al., 2008; WHO, 2012a). In the United States, the Food, Drug, and Cosmetic Act dictates a penalty of 1 year in prison, a fine of no more than $1,000, or both (Donaldson, 2010). Even repeat offenders are punished with no more than 3 years in prison or a fine of $10,000 (Donaldson, 2010). Considering that the profit margin for falsified drugs runs in the billions, the risk-to-profit

BOX 4-5
Manuel Calvelo

From 2005 to 2008, Manuel Calvelo operated internet pharmacies selling misbranded and falsified drugs for sale without prescription (DOJ, 2011). Calvelo sold $1.4 million worth of drugs on websites such as allcheapdrugs.com, cheapdrugspharmacy.com, and trustgeneric.com. He offered more than 40 products including Viagra, Zoloft, Lipitor, Cialis, and Xanax (Kake.com, 2011). Many were purported generic versions of patent-protected heart attack, stroke, and diabetes medications (PSM, 2011b).

Calvelo, a Belgian citizen, operated his business across borders. His customer service call center was in the Philippines; he paid his employees through wire transfers from Costa Rica, the Philippines, and the United States. Internet companies in Ohio and Kansas hosted his websites and he received payments through Dutch credit card processors from mostly American customers (DOJ, 2011).

In 2007, an undercover agent from the FDA's Office of Criminal Investigation bought drugs from Calvelo's websites (DOJ, 2011). These drugs appeared legitimate. Chemical testing, however, proved they were fake (PSM, 2011b). The agent later posed as a pharmaceutical wholesaler looking to establish an internet pharmacy (PSM, 2011a). Calvelo described the internet pharmacy scheme and the details of his operation to the agent (DOJ, 2011).

Calvelo was arrested in Costa Rica and extradited to Kansas. In January 2011, he plead guilty to one charge of conspiracy to commit drug trafficking and one charge of conspiracy to defraud the United States (DOJ, 2011). According to Patrick Holland, the special agent in charge of the FDA's Office of Criminal Investigation's Kansas City Field Office, "The investigation and [Manuel Calvelo's] sentencing reflect the seriousness of importing counterfeit and misbranded pharmaceutical drugs into the United States" (DOJ, 2011). Calvelo was sentenced to 48 months in prison and, as part of his plea, agreed to pay $1.4 million in fines (DOJ, 2011; Kake.com, 2011).

analysis favors the crime. Table 4-5 shows the penalties for falsifying medicines in a selection of countries. The leniency in many countries may be a function of outdated laws. Tables 4-6 and 4-7 show penalties for patent and trademark infringement, which are dealt with more severely in some countries.

Stricter and more consistent penalties could do much to fight the public health crime of producing and trading fake medicines. Chapter 7 discusses this solution in more detail, describing how a global code of practice could encourage consistent strict minimum punishments for these offenses.

REASONS FOR BOTH

As Chapter 1 explains, falsified and substandard medicines overlap a great deal. Much as poor-quality drugs are often both falsified and substandard, some potentiating factors encourage both kinds of problems. The high demand and erratic supply of drugs, weak regulatory systems, and lack of political will contribute to the trade on both falsified and substandard drugs.

Expense and Scarcity

Medicines are what economists describe as a comparatively inelastic good (Arnold, 2008); changes in the unit price of the medicine have proportionately little effect on the demand (Siminski, 2011). Price inelasticity, combined with a high relative price, make medicines a major expense for patients around the world. In the United States, health expenditures on medicine rise sharply in middle life and average between $1,000 and

Key Findings and Conclusions

- The demand for medicines is relatively consistent, though the supply is not. The private medicines market can be expensive and drug scarcity drives up prices.
- Reducing the costs and increasing the availability of medicines would remove some of the financial incentive to produce falsified and substandard drugs.
- A robust generics market can keep drug prices down, but there are cost barriers to market entry for many good-quality generics companies. A more straightforward registration and application process would reduce burdens on industry and regulators.
- Falsified and substandard medicines circulate because of weaknesses in the regulatory system. Regulators in low- and middle-income countries need training, equipment, and technology, as well as guidelines for strategic decisions about what to invest in first.
- In countries where state and federal governments share regulatory oversight, the division of responsibility is not always clear. Substandard drug production at the New England Compounding Center happened because of insufficient clarity between state and national responsibilities.
- Awareness of the problem of substandard and falsified medicines is uneven. Patients and providers need accurate information about the risks, communicated in way that empowers them to take reasonable precautions to protect their safety.

$2,000 per person per year after age 45 (Paez et al., 2009). The cost of medicine is even more of a burden in low- and middle-income countries, where it accounts for 20-60 percent of health spending, and 90 percent of the population pays for medicine out-of-pocket (Cameron et al., 2008; WHO, 2004a,b).

The drug market is not stable; both price and supply fluctuate. Sometimes the supply falters because of shortages in the raw materials, as in 2004 when increased demand for artemisinin, combined with a poor *Artemesia annua* harvest, drove up the price and led to stock-outs (Kindermans et al., 2007; Newton et al., 2006b; Pilloy, 2009). More generally, drug supply problems are driven by the economy. In the United States, for example, manufacturers sometimes stop producing products with low profit margins, such as sterile injectables—inexpensive products that are complicated to make (Hoffman, 2012). Manufacturers also can lose interest in a drug after its patent expires, when revenues from the product drop (Hoffman, 2012). Although the United States has a more stable drug supply than most developing countries, there have been regular shortages for the past 15 years, especially among injectables, cancer drugs, and antibiotics (Hoffman, 2012).

Drug shortages are more common in developing countries (MDG Gap Task Force, 2008). Survey data from the WHO and Health Action International suggest that although medicines may be available free or cheaply in public health centers, these centers often do not have the medicines needed; availability is generally better in the private sector but for a much higher price (Cameron et al., 2008; MDG Gap Task Force, 2008). Figure 4-3 shows that although private-sector outlets have a higher percentage of drugs available than public-sector ones, there is still a great deal of unmet need. A month's course of the lowest-priced generic ulcer medication, for example, is still more than 3 days' wages for a low-paid government worker in much of Africa, Eastern Europe, and the Middle East (Cameron et al., 2008).

Reducing the costs and increasing the availability of medicines would remove some of the financial incentive to produce and procure falsified and substandard medicines. If patients had a plentiful supply of reliable, affordable medicines, there would be less need to shop at unregulated gray markets.

The WHO has recommended generic substitution as a way to keep medicines costs down (MDG Gap Task Force, 2008), but this depends on a supply of high-quality generic medicines on the market. For generic manufacturers, companies that generally run on low margins, the costs of proving bioequivalence and preparing a manufacturer's dossier for regulatory review can be prohibitive to market entry (Lionberger, 2008). Different regulatory authorities have different, often widely divergent, requirements for establishing bioequivalence (Mastan et al., 2011). To complicate the

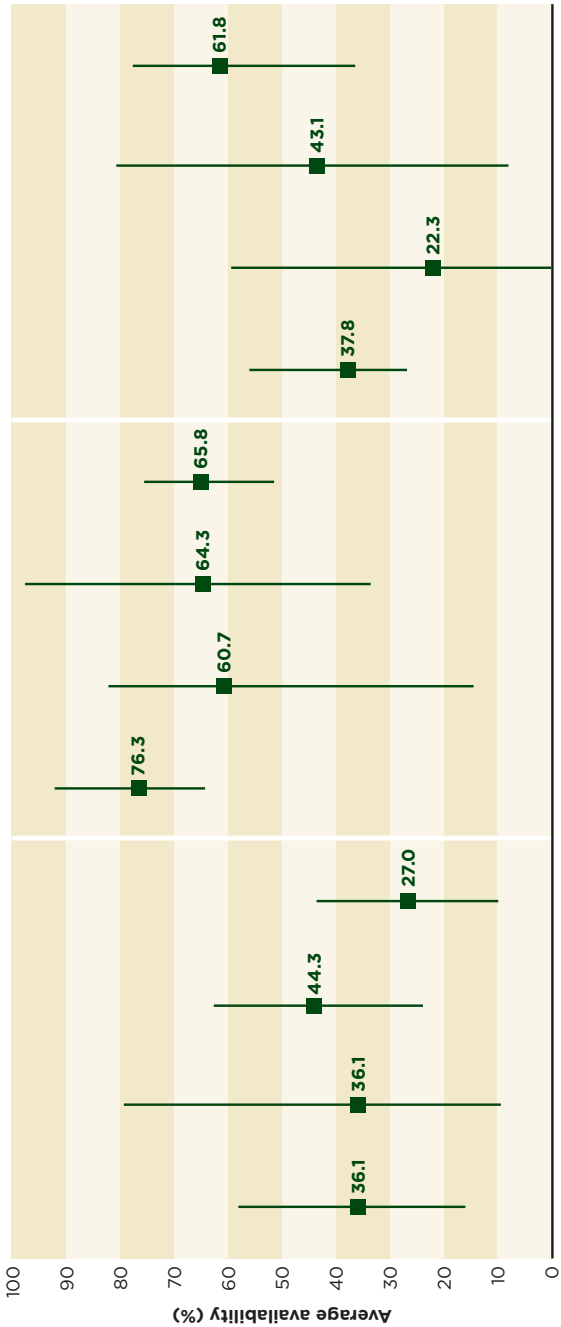

FIGURE 4-3 Average of country-level mean percentage availability of medicines by World Bank income group. Data are mean (maximum/minimum).
SOURCE: Cameron et al., 2008. Reprinted from the *Lancet* with permission from Elsevier.

problem, many small regulatory authorities lack the technical depth to evaluate the bioequivalence data that generics manufacturers submit (Hill and Johnson, 2004).

Reducing the Costs of Market Authorization

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together industry experts and regulators from Europe, Japan, and the United States to promote harmonized product registration requirements (ICH, 2010). To this end, ICH developed the Common Technical Document, a common application for medicines registration (ICH, 2012). The WHO has published guidance on preparation of generic product dossiers in keeping with the Common Technical Document format (Rägo, 2011; WHO, 2011). The committee believes this format could be useful to regulators and generics companies in low- and middle-income countries.

The use of a common form has made drug registration more efficient in Europe (Brousseau, 2012; ICH, 2010; Sahoo, 2008). It also controls the demands that registration puts on manufacturers. Harmonized applications also give regulators a common format to discuss their product registration process. Like sharing inspections and other harmonization efforts, the use of the common document increases efficiency and promotes a common language among regulators.

Recommendation 4-3: Regulatory authorities in low- and middle-income countries should use the International Conference on Harmonisation Common Technical Document format for product registration to better harmonize their procedures and reduce application costs for manufacturers. To the same end, they should also conduct joint inspections and use a common inspection report.

A more robust generic drug market in low- and middle-income countries could help prevent the drug shortages and price spikes that encourage the sale of poor-quality products. Regulatory authorities can work to better harmonize their procedures, thereby improving their own efficiency and reducing barriers to market entry for good-quality generics manufacturers. The use of the ICH Common Technical Document format for registration would ease the regulatory burden on generics companies. Regulators also reap a spillover benefit of more convergent regulatory systems without negotiating cumbersome mutual recognition agreements. The Singaporean drugs regulatory authority has promoted the common format, citing its ease of use and the way it facilitates sharing information among other regulators in the region (Poh, 2011). Similarly, Southeast Asian companies benefit

from the common format which allows them to prepare submissions for several countries at once (Poh, 2011).

The cost of bioequivalence testing runs from $50,000 to $200,000 (GIZ, 2012). Bioequivalence testing also requires sophisticated laboratories that are not available in many countries. This baseline cost to generic companies does not include several person-months of staff costs for revising registration application data into a new dossier. The costs of market authorization are prohibitively expensive, especially for entry into a small country's market. When the overwhelmed regulatory authority will allow it, companies avoid the expense by submitting no proof of bioavailability; others falsify bioavailability data (Silverman, 2011).

Evidence suggests that these high costs keep generics companies out of the market and increase costs to the consumer (Mastan et al., 2011; Rawlins, 2004). Even multinational, innovator pharmaceutical companies struggle to convert applications between FDA and EMA formats. A 1996 industry study estimated that converting applications took between 2 and 10 months and significant staff time and expense (Molzon, 2009). Different standards for bioequivalence assessment also encourage the problem of widely divergent national drug quality standards (Mastan et al., 2011).

If the application and registration process were more straightforward then more good-faith companies could enter the market, increasing the supply of reliable drugs and controlling costs. The committee also believes that a consistent use of the common registration format could further the cause of regulatory harmonization, which would improve the drug regulatory systems in low- and middle-income countries. Harmonization also controls the burdens regulation puts on manufacturers; shared inspections are more efficient and less disruptive to industry. Generics companies, which generally have fewer staff than innovator companies, are disproportionately disturbed by frequent inspections.

Weak Regulatory Systems

A competitive generics market benefits consumers, as does a rigorous and unpredictable inspection regime (Mackintosh et al., 2011). In many developing countries, lack of confidence in the regulatory system breeds low enthusiasm for generic medicines (Hassali et al., 2009; Kaplan et al., 2012; Russo and McPake, 2010). Doctors and patients may perceive these products as lower quality (Chua et al., 2010; Gossell-Williams, 2007). An influx of generic medicines will only reduce the circulation in falsified and substandard drugs when there is a system to assure consumers of medicines quality. In their review of policy actions to promote generic medicines, Kaplan and colleagues conclude that a functioning medicines regulatory

authority is a necessary condition for a robust generic medicines market (Kaplan et al., 2012).

The drugs regulatory authority has the ultimate responsibility for the quality of medicines in the country. That includes registering medicines, issuing licenses and market authorization, postmarket surveillance, quality control testing, oversight of drug trials, and manufacturer and distributor inspections (IOM, 2012; WHO, 2010a). The regulatory authority also provides health workers and the public with accurate information on the rational and safe use of medicines and punishes illegal trade in drugs (WHO, 2012b). This range of responsibilities requires significant technical depth in staffing and political will to enforce regulations. Staffing shortages are often a problem in the public sector in low- and middle-income countries, where regulators are poorly paid and not well respected (IOM, 2012).

Staffing shortages at the regulatory authority are a particularly serious problem in India and China, two main pharmaceutical producing nations with massive industries to oversee. In 2003 the Mashelkar Commission estimated about 5,877 licensed manufacturers in India; other estimates cite as many as 20,000 Indian drug manufacturers, some very small (Government of India, 2003; KPMG International, 2006). In any case, only 250 to 300 of them are major producers (KPMG International, 2006). China has a comparatively more manageable 3,500 companies, down from roughly 5,000 in 2004; the reduction is partly the result of heightened enforcement in the wake of a series of drug contamination scandals (Reuters, 2008).

The pharmaceutical industry in both countries is exceptionally fragmented. The top 10 pharmaceutical companies in India cover about 30 percent of the domestic market (KPMG International, 2006); in China the top 10 companies account for only 10 percent (Sun et al., 2008). In contrast, the top 10 innovator pharmaceutical companies control about 42 percent of the international market (Sun et al., 2008). Inspecting and licensing so many factories would be an overwhelming task for a well-funded regulatory agency with sufficient staff. In both China and India, the understaffed provincial authorities oversee licensing and inspecting manufacturers, with uneven results. In 2007 a Chinese provincial regulator issued 67 forged manufacturing licenses for a bribe (Liu, 2010). Indian regulators sometimes approve medicines without trials or valid expert review and authorize irrational, even dangerous, fixed-dose formulations of multiple active compounds (Vaidyanathan, 2012). Drugs that neighboring countries ban are often available in India because the regulatory agencies cannot enforce bans or execute recalls (Shaji and Lodha, 2010).

There are similar problems in less industrialized countries. A WHO survey of 26 drug regulatory authorities in sub-Saharan Africa found that only one country's regulator published guidelines on good distribution, while only 20 percent published internationally rigorous manufacturing practices

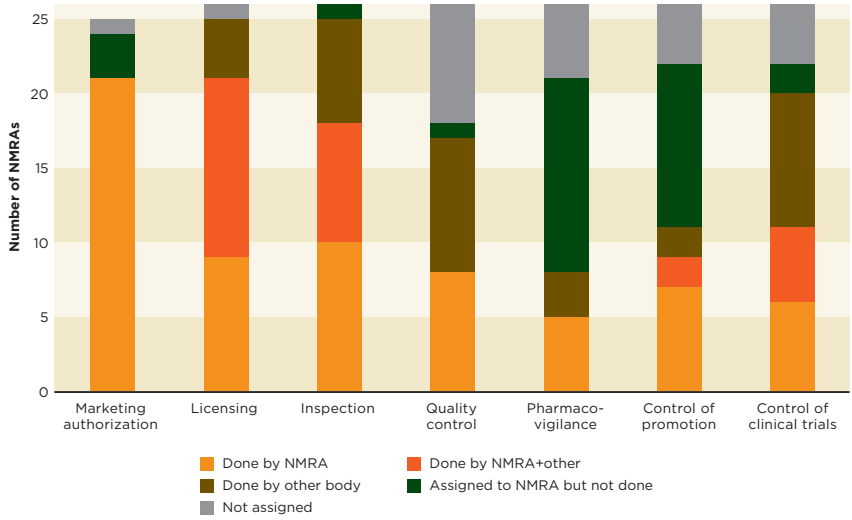

FIGURE 4–4 Number of sub-Saharan African countries out of 26 surveyed meeting the main functions of a regulatory authority.
NOTE: NMRA = National Medicines Regulatory Authority.
SOURCE: WHO, 2010a.

(WHO, 2010a). The same study found that several regulatory authorities grant licenses and renewals with no inspections, that operating procedures for conducting inspections were woefully weak, and that 35 percent of the regulatory authorities have no legal authority for inspections (WHO, 2010a). Figure 4-4 shows the number of agencies out of the 26 surveyed that can perform drug regulatory functions. All of these weaknesses allow for falsified and substandard drugs to circulate. As one of the participants in the WHO study explained, "The illicit medicines market has become a real plague. . . . All therapeutic classes can be found, including psychotropic medicines, and there is no national strategy to combat this situation" (WHO, 2010a, p. 16).

Governments in low- and middle-income countries need a strategy to act against falsified and substandard medicines. Any viable solution will include strengthening the drug regulatory system, including building the inspectorate, enforcing quality standards, and licensing in accordance with international standards. Without a competent regulatory authority to inspect wholesalers, distributors, and manufacturers, opportunities to corrupt the drug supply abound. Box 4-6 describes a patient safety disaster following the disbanding of the Pakistani national regulatory authority.

A 2012 Institute of Medicine report called for greater international investment in building food and drug regulatory systems in developing countries and for an international training and credentialing system for

BOX 4-6
Dissolution of the Pakistani Drug Regulatory Authority

Over the course of several weeks in January 2012, more than 120 patients in Lahore, Pakistan, died of drug overdoses and hundreds more suffered adverse reactions after being treated with contaminated heart medicine at the Punjab Institute of Cardiology (Arie, 2012). The drug responsible was Isotab (isosorbide mononitrate, 20 mg), manufactured by Efroze Chemical in Karachi, Pakistan (Arie, 2012). Each Isotab tablet contained isosorbide mononitrate, as well as 14 times the normal dose of the antimalarial drug pyrimethamine. The overdose caused rapid bone marrow, white blood cell, and platelet depletion (BBC, 2012). The drug's packaging did not contain dates of manufacture or expiration, and the drugs were given to patients for free (Arie, 2012). Drug pricing was a concern at Punjab Institute of Cardiology. Anonymous sources at the hospital reported significant pressure to buy the lowest cost drugs available. Under Pakistani law, when the lowest bidder does not win a sale, rejected firms can bring lawsuits against the hospital (BBC, 2012).

Pharmaceutical regulation in Pakistan is particularly weak. Though the government approved an independent drug regulatory authority in 2005, political tensions prevented action (Arie, 2012). In 2010, a constitutional amendment further debilitated regulation by abolishing the ministry of health. Provincial governments, many with weak infrastructures, were given sole responsibility for drug regulation. Manufacturers exploited the confused system by rapidly registering thousands of drugs (Khan, 2012).

Following the Isotab scandal, the Pakistan Supreme Court ordered action on the independent agency. Doctors have expressed doubts, fearing that insufficient regulatory expertise and ineffective execution will impede the new agency's success (Khan, 2012). Their concerns appear to be well founded. The new agency's board includes only one position for an expert in medicine or pharmacy (Khan, 2012).

Protesters in Lahore, January 2012.
SOURCE: Owasis Asam Ali, Demotix News.

regulators (IOM, 2012). This committee supports these recommendations. It also recognizes that the magnitude of the task facing these agencies is overwhelming and that governments need to make drug quality a priority, and then empower their regulatory agencies to improve.

Recommendation 4-4: Governments in low- and middle-income countries should support their regulatory agencies to develop strategic plans for compliance with international manufacturing and quality-control standards. In the least developed countries, international organizations should support their efforts.

International quality standards for drug manufacture depend on the competence of the national regulatory authority. Regulators in low- and middle-income countries need training, equipment, technology, and reference standards (IOM, 2012). The agencies' budgets do not allow for improvements in all these areas, and the scope of the needs can overwhelm the agencies, leading to inaction. It is important for regulators to make strategic decisions about what to invest in first. A strategic plan can help identify an organization's priorities and guide activities that advance these priorities (Tominaga, 2012).

The committee believes that making a strategic plan is feasible for almost all poor countries. The process of making the plan helps regulators advocate for better support from their ministers and identify places for donors to contribute. At a strategic planning workshop in 2010, for example, the Namibian health minister asked the regulatory authority to propose ways to build capacity in the agency and to advance harmonized regulatory systems in southern Africa (TIPC, 2010).

Agencies in the poorest countries should first enforce standards in manufacturing, wholesale, and retail. The WHO and more developed regulatory agencies should support these improvements. There is good precedent for such collaboration. The WHO prequalification program has a capacity-building function. As part of the program, regulators from low- and middle-income countries serve 3-month rotations at WHO headquarters (WHO, 2010b). Their rotations require close work with prequalification assessors and allow for sharing ideas about how to monitor manufactures (WHO, 2010b). A similar partnership among regulators could also be useful. Some regulatory agencies in emerging economies have made great progress in a relatively short time. These agencies are well positioned to help their counterparts in other developing countries set out their goals. For example, experts from the Brazilian drug regulatory agency, Anvisa, could work with their counterparts in Mozambique or Angola to help develop realistic plans.

A strategic plan for compliance with international standards can help reduce redundant work and fragmentation. Both industry and regulators

would agree to work toward the priorities identified on the strategic plan, and all work would be directly related to the plan, an openly shared document (Tominaga, 2012). For many smaller countries the plan should include a strategy for sharing work and pooling resources. At the regional level, the New Partnership for Africa's Development recently published a 5-year strategic plan for regulatory harmonization (NEPAD, 2011). This document identified the technical barriers facing African regulators, clarified the mission of the African Medicines Regulatory Harmonization (AMRH) project, and identified objectives for 2011-2015 (NEPAD, 2011).

Multilateral agencies, such as development banks, should support the development and implementation of strategic plans for compliance with international standards. The pharmaceutical market is international, and everyone has an interest in promoting global standards. There is precedent for such investment. The Bill & Melinda Gates Foundation, the British Department for International Development, the World Bank, and the WHO all support the AMRH program (AMRH, 2012). Donor agencies can do similar work, as USAID has in support of postmarket surveillance in Latin America, Southeast Asia, and Africa (Miarlles, 2011).

Regulators will welcome the strategic investments this planning would bring. Governments need to support these investments as well. Compliance with international standards will demand a wide range of activities, including research, education, supply chain management, and incentives for the private sector. The regulatory agency alone cannot effect change and will need government support to marshal the involvement of all stakeholders.

Developed country governments also need to improve support for their regulatory agencies. At the time this report was prepared, substandard injectable drugs caused a fungal meningitis outbreak in the United States, bringing the topic of drug regulatory oversight to the forefront of the U.S. political discourse.

Gaps in Regulatory Oversight

On September 21, 2012, the Tennessee Department of Health notified the Centers for Disease Control and Prevention (CDC) about an outbreak of meningitis caused by fungal infection through a contaminated epidural steroid injection from New England Compounding Pharmacy Center in Framingham, Massachusetts (CDC, 2012). By early 2013, the CDC had counted 693 illnesses and 45 deaths in 19 states from the contaminated drug (CDC, 2013). The FDA's October 2012 inspection report indicated gross violations of good manufacturing practices, including visible contamination of equipment and drug ingredients at the New England Compounding Pharmacy (FDA, 2012b).

The outbreak brought to light a gap in the U.S. regulatory system. The

FDA's MedWatch system had identified drug quality problems with methylprednisolone acetate, the steroid that caused the 2012 outbreak, at New England Compounding Center in 2002 and 2004 (Energy and Commerce Committee, 2012). The FDA and Massachusetts state inspectors uncovered sanitary violations in a joint inspection and issued the manufacturer a warning in 2006 (Energy and Commerce Committee, 2012). The problem is not confined to New England Compounding Center. In 2002, nonsterile practices at a South Carolina compounding pharmacy caused a similar, though smaller, outbreak (CDC, 2002). Since 2001, the FDA has issued 67 warning letters to various compounding pharmacies (Markey, 2012), but the FDA's authority over these organizations is unclear and has been for some time. In 1996, David Kessler, then FDA commissioner, testified that compounding pharmacies threatened to create "a shadow industry" of unregulated drug manufacture (Kessler, 1996).

In the United States, professional practice, including the practice of medicine and pharmacy, is regulated by the states. Compounding pharmacies, which were traditionally small operations that prepared custom drugs for individual patients, fall under state jurisdiction (Burton et al., 2012). Pharmacy councils have long resisted federal interference in their practice, including oversight of compounding pharmacies (Calvan, 2012; Markey, 2012). At the same time, enforcement of the Food, Drug, and Cosmetic Act, which controls the marketing and manufacture of medicines, is the FDA's responsibility. Large compounding pharmacies are in practice much closer to small manufacturers than pharmacies (Burton et al., 2012), though compounding pharmacies do not register with the FDA as manufacturers (Outterson, 2012). A 2007 bill aimed to increase FDA oversight of compounding pharmacies, but met the vociferous opposition of the International Association of Compounding Pharmacists and died in committee (Burton et al., 2012). Confusion over the regulation of compounding pharmacies was evident at congressional hearings on November 14, 2012 (Grady, 2012). *New York Times* reporter Denise Grady observed, "The hearing was titled 'The Fungal Meningitis Outbreak: Could It Have Been Prevented?,' but the question was never really answered" (Grady, 2012).

Disagreement over what authority the FDA has promotes a degree of paralysis. Neither the state of Massachusetts nor the FDA had clear control over the New England Compounding Center. Confusion about their responsibilities created a regulatory gap that the company exploited. Similar confusion causes regulatory gaps in other countries where national and local governments share responsibilities for drug regulation. In 2003, the Mashelkar Report raised concerns with Indian states' uneven implementation of drug regulations (Government of India, 2003). More recent testing and sampling confirms that drug quality is still more reliable in states with stricter regulations (Bate et al., 2009a). Brazil, China, Russia, and many

other large countries face similar problems (Mooney, 2010; Vashisth et al., 2012).

Lack of Awareness and Action

As Chapter 3 explains, there is a dearth of reliable estimates of the scope of the problem of falsified and substandard medicines. Without a clear picture of the extent of the problem, which products are compromised, and where the products surface, it is difficult to develop an appropriate prevention strategy and monitor progress. An insufficient understanding of the scope of the problem also contributes to a lack of awareness about substandard and falsified drugs among health workers and the general population. Increasing public awareness will not in and of itself decrease falsified and substandard medicines, because consumers cannot distinguish safe and unsafe medicine in the marketplace. However, public awareness is a useful way to drive political will for correcting the problem and to educate people on warning signs of compromised medicines.

Uneven Awareness

Starting in the early 2000s, medicines counterfeiting (as it was then called) has been the topic of some media attention. General awareness of the problem was still poor, however (Cockburn et al., 2005; Newton et al., 2006a). Reporting was "alarming[ly] low": between 2002 and 2004 the WHO received no reports of fake drugs from any member states (Newton et al., 2006a). This began to change in 2006 when the International Medical Products Anti-Counterfeiting Task Force (IMPACT) made raising awareness one of its main goals (Liberman, 2012).

IMPACT, and the larger debate about pharmaceutical fraud that it was a part of, appears to have had success in raising awareness of the problem in some parts of the world. A 2010 Gallup poll in sub-Saharan African countries found that the majority of the public in 15 of the 17 countries surveyed were aware that fake medicines were a problem (see Table 4-8) (Ogisi, 2011). The leadership of drugs regulators in Nigeria, one of the largest and most influential African countries, might have contributed to the public consciousness in Africa (see Box 4-7). More recently, Interpol launched an awareness campaign featuring South Africa's Yvonne Chaka Chaka and Senegal's Youssou N'Dour, two of the continent's biggest celebrities (Interpol, 2011). Awareness of the problem is also growing in Southeast Asia (Christian et al., 2012a; Gleeson, 2012).

Other research suggests gaps in awareness, especially among the poorest people in society. A qualitative study of Sudanese policy makers and pharmacists suggested that awareness of counterfeit products is lowest

TABLE 4–8 Response to the Question "Are You Aware of the Presence of Fake Medicine in This Country?"

Country	% Yes
Cameroon	91
Sierra Leone	83
Nigeria	83
Liberia	79
Ghana	74
Mali	74
Central African Republic	72
Burkina Faso	71
Uganda	70
Zimbabwe	69
Tanzania	66
Senegal	65
Kenya	63
Niger	62
Chad	58
Botswana	32
South Africa	25

NOTE: Data collected by Gallup in 2010. By *fake medicine*, we mean a product that looks like the real one but doesn't provide the same effect and could even have bad side effects.

SOURCE: Ogisi, 2011.

among the poor and people living in remote areas (Alfadl et al., 2012). Participants at overseas site visits for this study mentioned similar patterns in many developing countries. Often, well-educated urban consumers understand the threat of fake drugs and take precautions to avoid them. The poorest patients, and those living in areas with few to no reliable pharmacies, are often the least aware. Moreover, as Chapter 5 will discuss, they often have no choice but to buy medicines in the open market or have no money to buy from a registered pharmacy.

It is not clear how well informed populations in other parts of the

BOX 4-7
A National Awareness Campaign in Nigeria

In February 2005, the Nigerian drugs regulatory agency launched a national awareness campaign about fake medicines in Nigeria (Akunyili, 2005). The success of this program may account for Nigerians' high (83 percent) awareness of the problem (Ogisi, 2011).

The awareness campaign had several pieces. The agency broadcast short public service announcements on television and radio in English and local languages. "There is a development," a young businessman tells an obvious kingpin in one television piece; "you can no longer use my warehouse or any of my outlets for the distribution of your fake drugs!" (NAFDAC, 2011). The piece ends with the villain arrested at gunpoint to voiceover assurance of the agency's commitment to protect the Nigerian public.

Other pieces of the public awareness campaign intended to change consumer behavior (Akunyili, 2005). The regulators reasoned that if consumers were informed about falsified medicines and empowered to make safe choices, they would. To this end, they published lists of known fake products and photos illustrating warning signs in daily newspapers (Akunyili, 2006; Raufu, 2006). High school consumer safety clubs helped enlist youth in the cause. Since 2002, the agency has sponsored an essay contest on medicine safety for students, awarding cash prizes to the winners and computers to their schools (Akunyili, 2006).

A public health campaign poster from Nigeria.
SOURCE: Jack, 2007. Reprinted with permission from BMJ Publishing Group LTD.

world are about falsified and substandard drugs. People in developed countries, who have long taken medicines regulation for granted, are among the least knowledgeable. An Inter-Press Service story reported that 20 percent of Western Europeans did not consider it dangerous to circumvent traditional pharmacies to buy medicine (Stracansky, 2010). The same behavior has long been normal in the United States, where pharmacy tourism to Canada and Mexico has been common since the 1970s (Rabinovitch, 2005). Chapter 5 will discuss the internet pharmacies that have largely replaced in-person cross-border shopping.

Public Action

Educating the public on the problems of falsified and substandard medicines is important, but only insomuch as education empowers people to act. In an international site visit for this report, a procurement agency informed the IOM delegation that when they uncover manufacturers making substandard drugs they do not report the offense to the authorities. The reasons they gave included doubt that the regulator would act on their information and fear of litigation.

Similar attitudes may underlie a lack of reporting of adverse drug reactions among health workers in developing countries. Health workers are the first line for monitoring the safety of medicines. Their role in surveillance is important in low- and middle-income countries, where falsified and substandard drugs are common, and less than 27 percent have functional pharmacovigilance systems (Pirmohamed et al., 2007). Reporting of adverse drug events is generally low in these countries (Chedi and Musa, 2011; Fernandopulle and Weerasuriya, 2003; WHO, 2002b). Few staff are trained in pharmacovigilance, a practice sometimes seen as adding to the responsibilities of already overworked health professionals (Olsson et al., 2010; Sharma and Ahuja, 2010).

The increasing awareness of falsified and substandard medicines could drive improved pharmacovigilance in developing countries. Awareness campaigns and investigative reporting reach health workers as well as they reach the rest of the public. There is also a need for targeted health worker education on falsified and substandard medicines, emphasizing the correct reporting channels health workers can use to confirm suspected cases of falsified and substandard drugs. Much useful work has been done on the first steps of this process; clinicians struggling to broach the topic with their patients can consult the World Health Professionals Alliance guidelines on how to inquire about suspicious medicines (see Box 4-8).

Chapter 3 describes governments' and drug companies' reluctance to share information on substandard and falsified drugs (Cockburn et al., 2005). Pharmaceutical companies fear damage to their branding from

BOX 4-8
Health Worker Guidelines

It is important for health care workers to query gently, by asking

1. *Where* patients will or did buy the medicine. Emphasis can be placed on the importance of buying medicine from a pharmacy or other known and reliable sources.

   For example: "Did you purchase the medicine from a known and reliable source?"

2. *What* patients should look out for when they buy medicines. It can be suggested that patients check the packaging, the product, and the patient leaflet when they purchase medicine.

   For example: "Was the packaging of the product intact, properly sealed, clearly labeled with dosing, manufacturer, batch number, and expiry date?"

3. *How* the medicine is expected to take effect. By explaining what should happen when patients take medicine, health professionals can help patients identify anything unusual.

   For example: "Did the medicine cause any unexpected side effects?"

4. *When* the first improvements in condition should be experienced. If a medicine is supposed to start relieving symptoms within 24 hours, for example, then patients should know, so that if the medicine does not take effect, then can notify their health professional.

   For example: "Has the medicine taken longer than anticipated to have an effect?"

SOURCE: WHPA, n.d.

rumors of poor quality, whereas governments can see such information as undermining confidence in the health system (Cockburn et al., 2005). These concerns are well grounded, and an appropriate communication strategy will convey accurate information is a way that is sensitive to all stakeholders. Falsified and substandard medicine is a sensitive and dynamic problem, and the public has a right to accurate information about it. This information can be presented in such a way as to empower the consumer to make safe choices and to build confidence in the regulatory system. A professional

communication strategy provides the best guarantee that sensitive information is conveyed clearly and well.

Recommendation 4-5: Governments and donor agencies should fund development of effective communication and training programs for consumers and health workers on understanding the quality and safety of medicines.

Falsified and substandard drugs are a potential threat around the world, though risk varies widely from country to country. Awareness of the problem also varies and may be most limited in countries with strong regulatory systems but where, because of the global drug supply chain, substandard and falsified drugs still reach consumers. An effective communication campaign should present accurate information in a way that empowers patients to protect their own health. For example, the FDA website discourages buying drugs from foreign websites (see Figure 4-5) (FDA, 2012c). The CDC website gives similar guidance, discussing poor-quality antimalarials and alerting prospective travelers to avoid buying drugs abroad (CDC, 2010).

Education and communication are feasible in rich and poor countries alike. Representatives of 200 WHO member states stressed the importance of educational initiatives for consumers and health workers at the first meeting of the WHO global mechanism against falsified and substandard drugs (WHO, 2012c). Many developing countries have already made headway in consumer education. Figure 4-6, for example, shows a Cambodian health education poster promoting licensed pharmacies. Similarly, as Box 4-7 explains, the Nigerian drugs regulatory authority improved public understanding of the problem with relatively simple steps: public service announcements, newspaper ads, and school essay contests. This kind of campaign is realistic in many low- and middle-income countries.

While information about the problem is important, it is also important to link this information to action. The messages communicated and the action promoted will vary by country or region. In many countries, the most useful messages will be about specific drugs and vendors. Buying antimalarials from street markets, for example, is a dangerous behavior in most of Africa and Southeast Asia. Chapter 5 discusses some of the safe medicine outlets that the communication campaigns could promote.

The most wide-reaching communication strategies make use of many channels, including print media, television, radio, the internet, mobile devices, and social media. Governments and NGOs have made good progress using these channels to promote understanding of the problem (Besançon, 2008, 2012; Elliot, 2012; FIP, 2011). Educated consumers may now be more receptive to messages about the correct appearance or taste of medicines, the normal responses to it, and possible side effects. Patients who

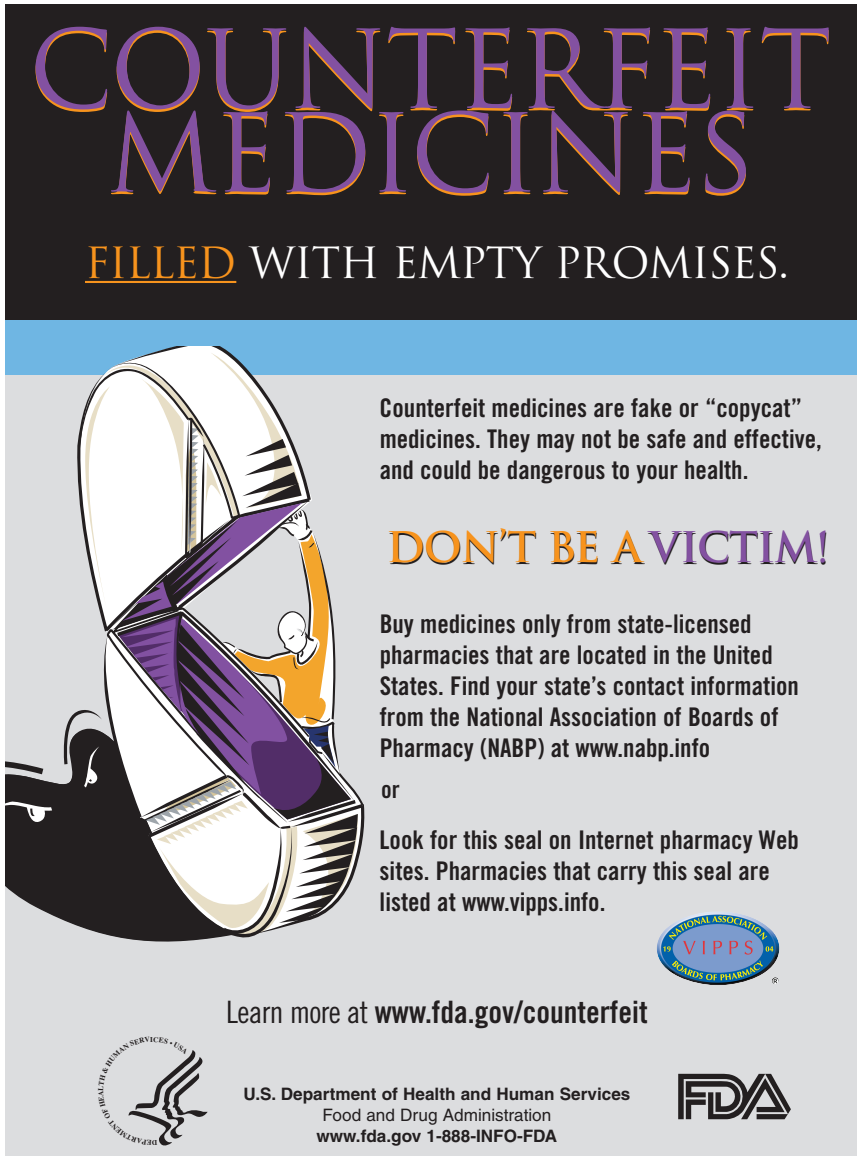

FIGURE 4-5 An FDA public service announcement that promotes the Verified Internet Pharmacy Practice certification discussed in Chapter 5. This is an example of an empowering consumer education message.

NOTE: The poster uses the term *counterfeit* broadly, the way this report uses *falsified*. See page 23.

SOURCE: FDA, 2012.

FIGURE 4-6 The English translation of a Cambodian poster encouraging consumers to buy medicines only from licensed pharmacies and to examine the drug's color, shape, and taste for abnormalities.

NOTE: The poster uses the term *counterfeit* broadly, the way this report uses *falsified*. See page 23.

SOURCE: U.S. Embassy, Phnom Penh, Cambodia.

understand the correct attributes of their medication will be better able to identify suspicious products.

Therefore, governments and donors should consider developing medicine checklists that remind patients of dangers and help them identify problem drugs. A checklist or authentication database might include the reasonable price range for the drug (thereby reminding people that low costs are suspicious); a check for sealed, complete packaging; a check for the correct shape and markings on the pills; and a check for other physical properties such as stickiness or hardness. Mobile phones might be the most efficient way to disseminate this information. Consumers could also use their phones to photograph suspicious drugs and relay the image to a central site for review. Mobile phones and the internet have a wide reach and will be useful tools for promoting such a checklist. Patients and providers could use mobile phones to access a database with information about poor-quality drugs.

Health workers are the first line of pharmacovigilance and will be point persons in any consumer education campaign. Their training should include information on falsified and substandard drugs. Providers should be made

more aware of their role in the postmarket surveillance of medicines, a new responsibility in many developing countries (Sharma and Ahuja, 2010). A health worker checklist might remind providers to ask patients for information about lack of response to treatment, slow response, and appearance of unusual symptoms. The list would also remind health workers about the proper channels for reporting an adverse event.

The next 10 years will see the introduction of many new drugs and vaccines in low- and middle-income countries (Kaufmann et al., 2011; Lienhardt et al., 2012). Messages of caution about dangerous medicines should not be presented in such a way as to scare people or to discourage appropriate use of medicines (Larson et al., 2011). To this end, awareness and communication campaigns could take some inspiration from successful vaccine safety campaigns (Leitmeyer et al., 2006; Mansour-Ghanaei et al., 2008). Awareness campaigns should also be tailored for their audience. Programs for policy makers would include a broader summary of the conditions encouraging the trade in falsified and substandard medicines, as presented in this chapter.

In summary, careless manufacturing, whether deliberate or accidental, causes substandard medicine. Making falsified medicines is driven by the interests of criminals, who weigh the millions of dollars in potential profits against low odds of getting caught. To complicate the problem, medicines are expensive and often scarce. There is a financial incentive to produce a poor-quality or imitation drug. These products circulate because national regulatory authorities are often poorly equipped to detect problems and act against them.

TABLE 4–5 Penalties for Falsifying Medicine*

Maximum Prison Sentences	Country	Maximum Civil Monetary Penalty (Quantified Penalties in U.S. Dollars)
Up to 6 months	Indonesia[a]	Up to $30
Up to 2 years	Tanzania[b]	Up to $57,000
Up to 3 years	Japan,[c] Malaysia[d]	Up to $40,000
	Canada[e]	Up to $5,000
	Lebanon[f]	Up to $30,000
	Singapore[g]	Up to $100,000
Up to 5 years	Jordan[h]	Up to $15,000
	France,[i] South Africa,[j] Switzerland[k,l]	$100,000 or more
Up to 10 years	Colombia,[m] Germany,[n] Peru[o]	Monetary penalty not disclosed
	Uganda[p]	Up to $2,000
	Pakistan[q]	Up to $5,000
	Argentina,[r] Cambodia[s]	Up to $15,000
	South Korea,[t] Taiwan[u]	$100,000 or more

* Additional penalties and fines may be associated with specific infractions.

[a] WHPA. 2011. Background document on counterfeit medicines in Asia. Paper read at WHPA Regional Workshop on Counterfeit Medical Products, Taipei, Taiwan.

[b] The Tanzania Food, Drugs and Cosmetics Act, 2003. (Tanzania). Part IV, Sec. 76 (2).

[c] WHPA. 2011. Background document on counterfeit medicines in Asia. Paper read at WHPA Regional Workshop on Counterfeit Medical Products, Taipei, Taiwan.

[d] Business Monitor International. 2010. Malaysia pharmaceuticals and healthcare report 2010. London: Business Monitor International.

[e] Food and Drugs Act (R.S.C., 1985, c.F-27). (Canada). Sec. 31 (a);(b).

[f] Ghosn, Z. 2008. *Lebanon launches campaign to counter fake drugs*. http://www.scidev.net/en/news/lebanon-launches-campaign-to-counter-fake-drugs.html (accessed October 4, 2012).

[g] Health Products Act (Chapter 122D). (Singapore). 2007. Part IV, Art. 16, Sec. 1 (b); 2 (b).

[h] Saba & Co. IP. 2009. *Jordan: Relentless efforts to curb counterfeit drugs*. http://www.sabaip.com/NewsArtDetails.aspx?ID=514 (accessed October 4, 2012).

[i] Institute of Research Against Counterfeit Medicines. 2012. *Tracking and condemning fake drug traffickers*. Institute of Research Against Counterfeit Medicines.

[j] Counterfeit Goods Act 37 of 1997. (South Africa). Art. 19, Sec. 1 (a);(b).

[k] Betts, A. B. 2010. Fight against counterfeit medical products: The Medicrime Convention and the Swiss experience. Presentation given at International Conference of Drug Regulatory Authorities, Singapore.

[l] Therapeutic Medicines Act. (Switzerland). (December 15, 2000). Chap. 8, Art. 86 (1) a-g.

continued

TABLE 4–5 *Continued*

Maximum Prison Sentences	Country	Maximum Civil Monetary Penalty (Quantified Penalties in U.S. Dollars)
Up to 15 years	Nigeria[v]	Up to $5,000
	Brazil[w, x]	Up to $98,000
	Kenya[y]	Up to 5x the value of the medicine
Up to 20 years	Grenada,[z] Mexico[aa]	$100,000 or more
Up to life imprisonment or death	China[bb, cc]	Up to 5x the value of the medicine
	India[dd]	Up to $20,000 or 3x the value of the medicine
	Philippines,[ee] United States[ff]	$100,000 or more
	Thailand[gg]	Up to $1,700

[m] Bate, R. 2012. *Phake: The deadly world of falsified and substandard medicines*. Washington, DC: AEI Press.

[n] Medicinal Products Act. (Germany). (2010). Chap. 17, Sec. 95 (3) 3.

[o] AEI. 2012. *The deadly world of fake drugs*. AEI.

[p] The National Drug Policy and Authority Act of 2003. (Uganda). Chap. 206, Part IV, Sec. 30.

[q] The Drugs Act, 1976. (Pakistan). Chap. IV, Sec. 27 (1);(2).

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[u] WHPA. 2011. Background document on counterfeit medicines in Asia. Paper read at WHPA Regional Workshop on Counterfeit Medical Products, Taipei, Taiwan.

[v] Counterfeit and Fake Drugs and Unwholesome Processed Food (miscellaneous provisions) Act of 1999. (Nigeria). Sec. 3 (1).

[w] Capell, K., S. Timmons, J. Wheatley, and H. Dawley. 2001. What's in that pill? *Bloomberg Businessweek Magazine*.

[x] Lei Nº 6.437 De 20 De Agosto De 1977. (Brazil). Tit. 1, Art. 2, §1º.

[y] The Anti-Counterfeit Bill, 2008. (Kenya). Part VI, Sec. 35 (a); (b).

[z] AEI. 2012. *The deadly world of fake drugs*. AEI.

[aa] Ley General De Salud, 2012. (Mexico). Titulo Decimo Octavo, Capitulo VI, Artículo 464 Ter. (I); (II).

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[cc] Jailing, D. 2011. China broadens scope of counterfeit drugs criminal prosecution, but definition still murky. Elsevier Business Intelligence.

[dd] Sinha, K. 2009. From Monday, spurious drug sellers can be jailed. *Times of India*.

[ee] Special Law on Counterfeit Drugs. (Philippines). 1996. Republic Act No. 8203, Cong. of the Philippines Metro Manila, 2nd sess., Sec. 8 (b); (e); (f).

[ff] Counterfeit Drug Penalty Enhancement Act of 2011, HR 3468. 112th Cong., 1st Sess., Sec. 2 (a); (b).

[gg] Thailand Drug Act, B.E. 2510 (1967). (Thailand). Chap. X, Sec. 117.

TABLE 4–6 Penalties for Patent Infringement*

Maximum Prison Sentences	Country	Maximum Civil Monetary Penalty (Quantified Penalties in U.S. Dollars)
No imprisonment for infraction	Grenada,[a] India,[b] Malaysia,[c] Pakistan,[d] Philippines,[e] South Africa,[f] Uganda,[g] United States[h]	Damages are recovered
	Taiwan[i]	Infringer must may patentee profits earned
	Jordan,[j] Nigeria[k]	Patentee may file a civil or criminal lawsuit
	China,[l] Peru[m]	$100,000 or more
	Mexico[n]	$80,000 or more
Up to 1 year	Brazil[o]	Monetary penalty not disclosed
	Canada[p]	Up to $500
	Singapore[q]	Up to $10,000
	Switzerland[r]	$100,000 or more

* Additional penalties and fines may be associated with specific infractions.

[a] Patents Act (Cap. 227). (Grenada). (May 16, 1898). Art. 20.

[b] The Patents Act, 1970. (India). Chap. XVIII, Sec. 108.

[c] Malaysia Patents Act. Amended by Act 1264 of 2006. (Malaysia). (August 16, 2006). Par. XII, Sec. 60 (1).

[d] Patents Ordinance, 2000 as amended by Patents (Amendment) Ordinance, 2002. (Pakistan). Chap. XVII, Sec. 61.

[e] Intellectual Property Code of the Philippines. (Philippines). (June 6, 1997). Part II, Chap. VIII, Sec. 76 (1); (2).

[f] Patents Act No. 57 of 1978. (South Africa). (April 26, 1978). Chap. XI, Art. 65 (3); (6).

[g] The Patents Act. (Uganda). (October 15, 1993). Part V, Sec. 26 (2).

[h] U.S. Patent Law, 35 U.S.C. § 284. (2007).

[i] Patent Act. (2011). (Taiwan). Sec. 7, Art. 97 (2); (3).

[j] Patent Law, No. 32. (Jordan). 1999. Art. 33.

[k] Patents and Designs Act (Chapter 344). (Nigeria). Sec. 25 (1); (2).

[l] Patent Law of the People's Republic of China. (China). No. 8. 11th Cong. (December 27, 2008). Chap. VII, Art. 63; 65.

[m] Peru Industrial Property Law. (Peru). (May 24, 1996). Tit. XVI, Art. 242.

[n] *Industrial Property Law*. (Mexico). (Last amended January 26, 2006). Chap. II, Art. 214 (I); (V).

[o] Law No. 9,279 of May 14, 1996. (Brazil). Tit. V, Chap. 1, Art. 183 (I).

[p] *Canada Consolidation Patent Act*, R.C.S., 1985, c. P-4. (Canada). (Last amended September 21, 2006.) Sec. 75 (a); (b); (c).

TABLE 4–6 *Continued*

Maximum Prison Sentences	Country	Maximum Civil Monetary Penalty (Quantified Penalties in U.S. Dollars)
Up to 2 years	Thailand[s]	Up to $13,150
Up to 3 years	Germany[t]	Monetary penalty not disclosed
	Lebanon[u]	Up to $33,000
Up to 4 years	Indonesia[v]	Up to $50,000
Up to 5 years	Cambodia[w]	Up to $5,000
	France[x]	Up to $650,000
	Japan[y]	Up to $100,000 with labor
	Kenya[z]	Up to $6,000
	Tanzania[aa]	Up to $300
5 or more years	Argentina[bb, cc]	Monetary penalty not disclosed
	South Korea[dd]	Up to $100,000 with labor

[q] Singapore Patents Act as amended by Act No. 2 of 2007. (Singapore). (April 1, 2007). Part XVIII, Sec. 99 (1).

[r] Loi fédérale sur les brevets d'invention. (Switzerland). (June 25, 1954). Tit. 3, Chap. 3, Art. 81 (1).

[s] Patents Act Consolidation. (Thailand). No. 3. (1999). Part VI, Chap. VI, Art. 85.

[t] Germany Patent Act. (Germany). (July 30, 2009). Part 9, Sec. 142 (1).

[u] *Patents Law of Lebanon*, Law No. 240. (Lebanon). (August 7, 2000). Chap. 2, Sec. 1, Art. 42.

[v] Law of the Republic of Indonesia Regarding Patents. (Indonesia). No. 14. 2001. Chap. XV, Art. 130.

[w] *Law on the Patents, Utility Model Certificates and Industrial Designs*. (Cambodia). 8th sess., 1st legis. (December 31, 2002). Chap. 7, Art. 133.

[x] Intellectual Property Code. (France). (July 1, 1992). Chap. V, Sec. II, Art. L615-14 (1).

[y] Patent Act (Act No. 121 of 1959). (Japan). Chap. XI, Art. 196-2.

[z] The Industrial Property Act, 2001. (Kenya). Part XVI, Sec. 109 (1); (2).

[aa] The Patents (Registration) Act. (Tanzania). Part XV, Sec. 70 (1).

[bb] Penal Code of Argentina. (Argentina). Law 11,179 (1984). Chap. IV, Art. 172.

[cc] Legal Intellectual Property Regime (Argentina). Law No. 11.723, Art. 71.

[dd] Patent Act (Act No. 950 of December 31, 1961, as last amended by Act No. 9985 of January 30, 2009). (Republic of Korea). Chap. XII, Art. 225 (1).

TABLE 4–7 Penalties for Trademark Infringement*

Maximum Prison Sentences	Country	Maximum Civil Monetary Penalty (Quantified Penalties in U.S. Dollars)
No imprisonment for infraction	Cambodia,[a] Germany,[b] India,[c] Pakistan,[d] Philippines,[e] Singapore,[f] South Africa,[g] Uganda,[h] United States,[i]	Damages are recovered
	Korea[j]	Up to $47,000
	China,[k] Taiwan[l]	Infringer must pay the trademark owner profits earned from the infringement or the amount of losses that the trademark owner has suffered
	Jordan[m]	Up to $8,500
Up to 3 days	Mexico[n]	Up to $70,000
Up to 1 year	Switzerland[o]	Up to $110,000
	Brazil[p]	Monetary penalty not disclosed
Up to 2 years	Argentina[q]	Up to $30,000,000
Up to 3 years	Lebanon[r]	Up to $0.40
Up to 5 years	Japan[s]	Up to $60,000 with labor
	Indonesia[t]	Up to $105,000

*Additional penalties and fines may be associated with specific infractions.

[a] The Law concerning Marks, Trade Names and Acts of Unfair Competition. (Cambodia). Chap. 8, Art. 27.

[b] Germany Trademark Law (as amended on July 16, 1998). (Germany). Chap. 3, Sec. 14 (6).

[c] The Trade Marks Act, 1999. (India). No. 47 of 1999. Chap. XIII, Sec. 135 (1).

[d] Trade Marks Ordinance, 2001. (Pakistan). Chap. V, Sec. 46 (2).

[e] Intellectual Property Code of the Philippines. (Philippines). (June 6, 1997). Part III, Sec. 156.

[f] Trade Marks Act (Chapter 332). (Singapore). Part III, Sec. 31.

[g] Trade Marks Act No. 194 of 1993. (South Africa). Part VIII, Sec. 34, (3) c; d.

[h] The Trademarks Act, 2010. (Uganda). Part VIII, Sec. 79 (4).

[i] U.S. Trademark Law of 1946. § 32, 15 U.S.C. § 1114 (2012).

[j] Trademark Act. (Korea). Chap. VI, Art. 67; 67-2.

[k] Trademark Law of the People's Republic of China. (China). October 27, 2001. Chap. VII, Art. 56.

[l] Kuo, Y., and J. Wong (2012). Taiwan overhauling the trademark law, Formosa Transnational.

[m] Abu Ghazaleh Intellectual Property (2008). *New amendments to Jordan's trademark law*. Retrieved December 28, 2012, from http://www.ag-ip-news.com/news.aspx?id=24580&lang=en.

[n] Arenas, A. (2012). Country correspondent: Mexico, Olivares & Cía.

[o] Federal Law of August 28, 1992 on the Protection of Trademarks and Indications Source (as last amended on March 24, 1995). (Switzerland). Tit. 3, Chap. 2, Art. 61.1 (a); (b).

[p] Industrial Property Law No. 9.279, of May 14, 1996 (as amended by Law 10.196 of February 14, 2001). (Brazil). Chap. 3, Art. 189.

[q] Law on Trademarks and Designations (No. 22,362 of December 26, 1980). (Argentina). Chap. III, Tit. 1, Sec. 31 (b).

[r] Resolution No.2385/1924 issued on January 17, 1924, (amended by the law of 31/1/1946). (Lebanon). Part 6, Chap. 2, Art. 105.

[s] Trademark Act (Act No.127 of April 13, 1959). (Japan). Chap. IX, Art. 78-2.

[t] Law of the Republic of Indonesia, No. 15/2001 Regarding Marks. (Indonesia). Chap. XIV, Art. 90.

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5

Weaknesses in the Drug Distribution Chain

The modern pharmaceutical supply chain is complex. Medicines are made from ingredients sourced from different countries. Final formulations are then exported. Packaging, repackaging, and sale can happen in many other countries. Drugs change hands many times between the manufacturer and patient; every transaction is an opportunity for falsified or substandard products to infiltrate the market. Changes to the drug distribution system could improve drug quality around the world.

This chapter gives an overview of the drug distribution chain, explaining differences between the systems in developed and developing countries. The drug wholesale system is a weak point where the licit and illicit supply chains mix. Better controls on the wholesale market could improve the security of the distribution chain. Drug tracking systems could also improve security by preventing products that leave the legitimate supply chain from returning to it. These solutions can improve drug safety as long as the supply chain does not disintegrate at the point closest to the patient. Disorganized drug markets, both real and on the internet, undermine regulatory checks on medicines distribution.

AN OVERVIEW OF DRUG DISTRIBUTION IN DEVELOPED AND DEVELOPING COUNTRIES

Figure 5-1 describes the drug distribution chain in developed countries, where most patients get medicine from a doctor's office or a licensed pharmacy or dispensary (Yadav and Smith, 2012). For example, in the United States about three-quarters of all pharmaceuticals are bought in retail

Key Findings and Conclusions

- A few national firms control most of the primary wholesale market in rich countries. In developing countries, hundreds, sometimes thousands, of firms control tiny shares of the same.
- Drug distribution chains in developing countries are often fragmented and complicated.
- The final leg of the drug distribution chain is exceptionally expensive and inefficient in developing countries.

pharmacies, about half of which are national chains or food stores with an internal pharmacy (Yadav and Smith, 2012). These vendors handle a wide variety of products sold in an even wider variety of packaging. Retailers in developed countries would find it logistically impossible to buy their stock, in its many different packages, directly from manufacturers (Yadav et al., 2012). Therefore, most vendors buy their inventory from pre-wholesalers and wholesalers.

The drug distribution system in low- and middle-income countries has the same basic steps as that described in Figure 5-1, but with more intermediaries between the manufacturer and patient (Yadav and Smith, 2012). Instead of having one coordinated distribution chain that reaches the whole country, there are many small chains and many small companies at every step (Yadav and Smith, 2012). Figure 5-2 describes the drug flow for public, private, and nongovernmental organizations, and their separate, but sometimes overlapping, intermediaries.

A comparison of Figures 5-1 and 5-2 and Table 5-1 illustrate some important differences in drug distribution in developing and developed countries. For example, a few large firms generally control the national wholesale market in developed countries. Cardinal Health, McKesson, and AmerisourceBergen distribute 90 percent of drugs sold in the United States; four or five major firms distribute to 90 percent of the market in Western Europe and Japan (Yadav and Smith, 2012). In developing countries, hundreds, even thousands, of companies control tiny shares of the drug wholesale market (Yadav and Smith, 2012).

Excessive fragmentation is an important difference between developed and developing countries' drug distribution systems. In developed countries, comparatively few large firms control the market and regulatory authorities require some chain of custody documentation. In low- and middle-income countries, the system is vastly more complicated. Sometimes multiple parallel distribution systems of varying efficiency run in the same country.

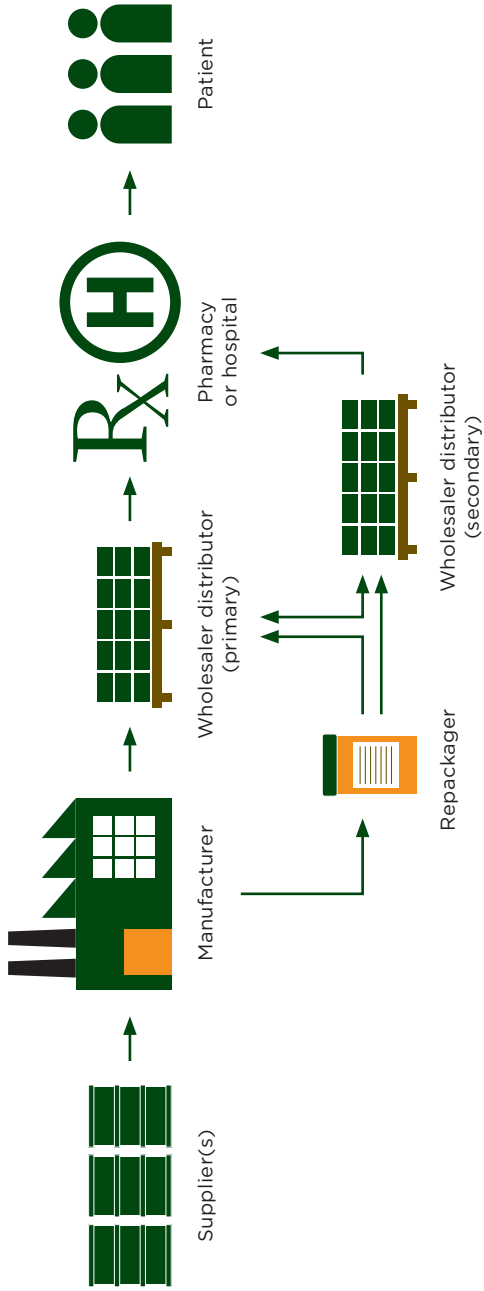


FIGURE 5-1 The drug distribution system.
SOURCE: FDA, 2011b.

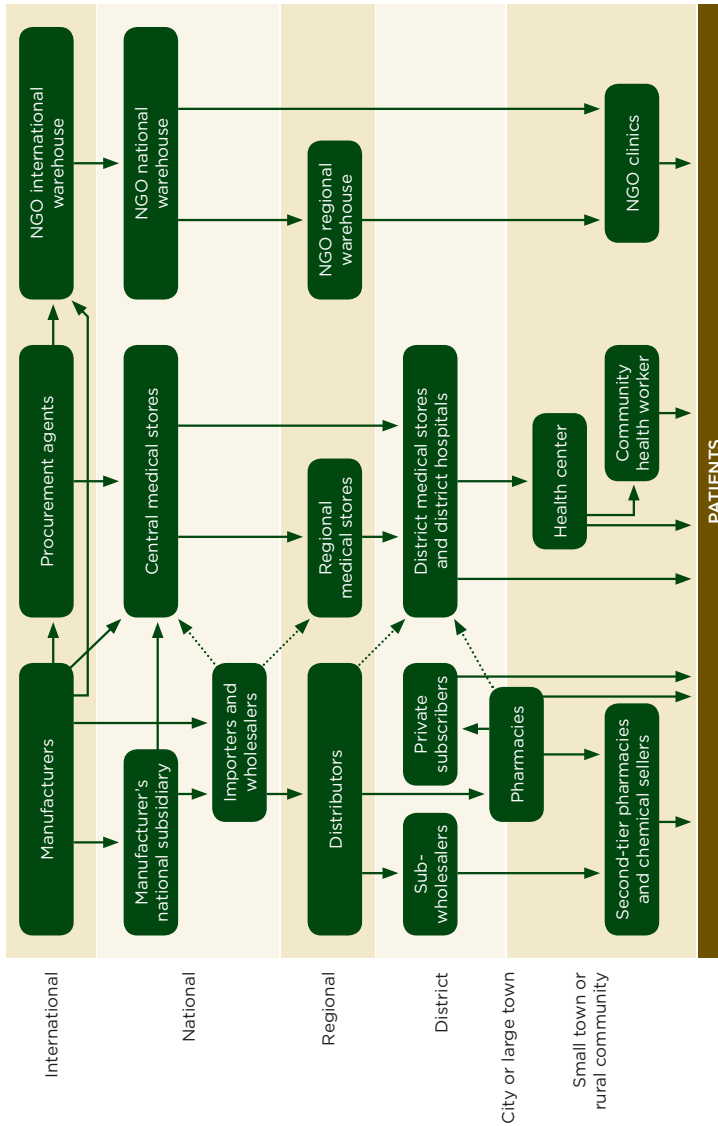


FIGURE 5–2 The private, public, and NGO drug distribution systems for essential medicines in developing countries.
NOTE: NGO = nongovernmental organization.
SOURCE: Yadav et al., 2011.

TABLE 5–1 Differences in Overall Structure of the Pharmaceutical Market in Developed and Developing Countries

Factor	Developed Countries	Developing Countries
Payer or reimbursement	Strong presence of public or private insurance companies and limited out-of-pocket expenditure.	Mostly payments are made out of pocket. Social health insurance systems are expanding in many emerging markets. Private insurance plans are also growing in some emerging market countries.
Regulatory structure	Strong, well-defined laws and overall good ability to enforce regulations.	Weak fragmented regulatory structures, ill-defined laws in some instances, and poor ability to enforce regulations.
Patented, generic vs. branded generic	The market for prescription drugs consists of patented drugs and generics.	Poor regulatory structure creates a strong market for branded generics (brand is used as a signal of quality by the patient).
Prescription adherence	Prescription drugs can only be dispensed with a formal prescription.	Retail drug shops often dispense medicines and also act as the first point of health care contact for many patients.
Balance of power in the system	Buyer (insurance companies or national health system) monopoly creates good balance of power between the manufacturer and the patients. In the United States, pharmacy benefit managers and drug formularies are commonly used as a means to ensure further balance of power.	Balance of power is tilted toward the manufacturer and the distribution channel. The large fraction of patients purchase with out-of-pocket funds and have little bargaining power.

SOURCE: Adapted from Yadav and Smith, 2012.

Box 5-1 describes the confusing drug distribution systems often found in humanitarian emergencies.

In OECD countries, private companies ship and transport almost all pharmaceuticals, but in developing countries, despite their vastly smaller tax base, the government does (Yadav, 2010). In sub-Saharan Africa, a government-owned-and-operated central medical store manages the distribution of drugs, transporting goods around the country in a government-owned fleet. Donors and developing-country governments favor this system, wherein the central store manager can neither hire people with business experience nor fire incompetent workers (Yadav, 2010). Inefficient supply chain management directly drives up costs and causes drug stock-outs in

BOX 5-1
Drug Distribution in Humanitarian Emergencies

A donated batch of Ringer's Lactate Infusions made its way to humanitarian aid workers in Darfur through a UN agency and other suppliers. Despite its many stops along the way, only at one of the final destinations did a volunteer doctor notice fungal spores contaminating the product (Caudron et al., 2008). The infusions had been distributed so widely and haphazardly that, despite a product recall, only 15 percent were ever collected (Caudron et al., 2008). Such problems are not uncommon during emergencies, when quality control throughout long supply chains becomes difficult.

Despite the good intentions of aid agencies, nongovernmental organizations (NGOs), and individual and corporate donors, the chaos inherent in humanitarian emergencies often leads to a proliferation of fake, substandard, and otherwise poorly regulated medical products. The dangers of poorly regulated drugs lead some bodies, such as the European Commission's Directorate-General for Humanitarian Aid, to stipulate that quality-assurance guidelines not be relaxed during emergencies, even though quality-assurance steps can slow down response (Pomatto and Schuftan, 2006).

After the tsunami in Sri Lanka, only 50 percent of the drugs donated had expiration dates on them; of that half, 5 percent had already expired or would expire within days; 62 percent of the medication labels were not in English, the language of the Sri Lankan health system (Mahmood et al., 2011). Such inappropriate drug donations cause serious problems because disposing of such drugs, especially in large quantities, is a lengthy and expensive project (Pomatto and Schuftan, 2006). After the 2000 floods in Venezuela, 70 percent of the drugs donated for humanitarian assistance needed to be destroyed, requiring the government to pay $16,000 to cover the extra personnel needed to sort the donations (Hechmann and Dune-Birouste, 2007).

During emergencies, little about patients, their diagnoses, or medical history is collected at most health facilities. Drug quality signals can be difficult to spot when infrastructure is disrupted: Patients are seen quickly and only minimal information is recorded. NGOs often arrive with few or no pharmacists on staff, and although local health workers may be aware of substandard and falsified drugs, visiting doctors often are not (Villacorta-Linaza, 2009).

The World Health Organization published its "Guidelines for Drug Donations" in 1996 after particularly problematic donations during the Bosnian War (Berckmans et al., 1997; Hechmann and Dune-Birouste, 2007). At times the guidelines are followed closely; for example, humanitarian emergencies in East Timor and Gujarat State saw few inappropriate donations (van Dijk et al., 2011).

low- and middle-income countries (Yadav, 2010). As Chapter 4 explained, this drug scarcity in turn creates a vacuum for poor-quality products to fill.

Of course, donor demands alone do not drive the costs of supply chain management in developing countries. It is expensive to transport products over rough terrain with poor roads. In India, for example, nearly 70 percent of the population lives in rural areas, where the health posts may be few and lacking in staff, electricity, and supplies (Langer and Kelkar, 2008). The costs of drug distribution in India are two to three times greater than in the United States or the European Union, despite vastly lower labor costs (Langer and Kelkar, 2008). Supply chain managers are always concerned with the last-mile problem: the disproportionately expensive and inefficient final leg on the distribution chain. In developing countries, the last mile is exceptionally long, extending to sparsely populated villages far from a paved road and farther from a supply center (USAID, 2011).

Managing the drug distribution system in developing countries means containing the costs of the last mile, moving medicines to patients quickly, and keeping records of all transactions between the manufacturer and the consumer. The first step on this chain is the drug wholesale market. Around the world, drug wholesale is a common point of vulnerability to falsified and substandard medicines.

THE WHOLESALE SYSTEM

There are two kinds of drugs wholesalers: primary wholesalers who have written distribution contracts with manufacturers and buy directly from them, and secondary wholesalers who buy from other intermediaries. In some countries, including the United States, there are also large regional wholesalers (Fein, 2012; White and Bothma, 2009). Regional wholesalers may be primary or secondary wholesalers (Fein, 2011). They often serve independent pharmacies or hospitals and may have strong distribution networks (Levy, 2006).

As Figure 5-1 suggests, the distinction between the primary and secondary wholesalers is not always clear. Primary wholesalers may, for example, buy products from secondary wholesalers as well as manufacturers (Ziance, 2008). The back-and-forth sales are common among drug wholesalers, who buy and sell medicines to accommodate market demand. That is, when they see a medicine is scarce in one region, they can buy the same medicine from other wholesalers that may be flush with it. The markets are constantly fluctuating; products change hands many times.

Sometimes secondary wholesalers fill a void; they supply to rural pharmacies or markets that national or regional wholesalers do not reach. But they choose stock based on demand forecasts, price, margin, and their customers' willingness to pay (Yadav, 2009). The costs of the transactions

Key Findings and Conclusions

- The U.S. drug wholesale market is made up of a combination of primary and secondary wholesalers. There are three major national wholesalers, a few regional wholesalers, and thousands of secondary wholesalers.
- Secondary wholesalers are the weakest point in the U.S. pharmaceutical distribution chain.
- Wholesalers buy and sell drugs in response to market demand, repeatedly repackaging products. In wholesale repackaging, illegitimate products can gain authentic packaging, and clean, authentic packaging is removed and not always destroyed.
- In the United States, state pharmacy boards or other state agencies license wholesalers. Their licensing requirements vary widely. Unscrupulous wholesalers seek out states with the most lenient requirements and move from state to state when caught in violations.
- There is no national database on drug wholesalers.
- Raising the minimum standards for drug wholesale in the United States could build momentum for increased control of the drug wholesale market in low- and middle-income countries.

required when dealing with many suppliers and their generally poorer bargaining power give the secondary wholesalers weak incentives to stock a wide variety of products or brands (Yadav, 2009).

Wholesalers may sell and resell medicines repeatedly among themselves before filling a pharmacy order. Wholesalers often repackage products with every sale, or at least repackage individual containers for final sale (Catizone, 2006; Laven, 2006). Through a process called salting, legitimate and fake drugs are mixed at wholesale, and in the wholesale repackaging, the fake products gain authentic labels (Donaldson, 2010; Liang, 2006). Salting can be done unknowingly, such as when primary wholesalers buy from other intermediaries, accidentally launder fake products, package them in authentic labels, and send them to pharmacies (Spies and VanDusen, 2003). In repackaging the manufacturer's expensive fraud-protection packaging can be removed, and batch numbers reprinted (Satchwell, 2004). Not only does this interfere with tracking requirements, but it leaves the wholesaler repackagers with clean, unused packaging that is not always destroyed (Satchwell, 2004).

Manufacturers usually have no distribution agreements with secondary wholesalers (Ziance, 2008). The firms may trade in many kinds of products other than pharmaceuticals. Their staff are not required to show skills

in pharmaceutical warehousing and management, often with disastrous consequences (Ziance, 2008). In 2001, for example, a falsified version of Epogen, one of the most expensive drugs in the Medicare formulary, killed a 16-year-old boy in New York (Gressit, 2007; Ziance, 2008). Eleven secondary wholesalers had traded the Epogen that killed him (Engelberg et al., 2009; Gressit, 2007; Whoriskey, 2012). Though it is impossible to recreate the drug's exact path, it was briefly stored in a drinks cooler above a Florida strip club (Brown, 2005).

Small secondary wholesalers act negligently in part because they do not have the reputational risks that major national or regional wholesalers do. There are thousands of secondary wholesalers in the United States, all legally supplying to pharmacies, the product of lax licensing requirements (Appleby, 2003). In a recommendation to the state legislature, a Florida grand jury described some of the states' drug wholesalers as "uneducated, inexperienced, . . . rank amateurs, many with criminal records" (Appleby, 2003). As the grand jury description implies, many of these companies are looking to increase their profits at any cost.

These companies exploit problems in the regulated drug market, such as drug shortages. Hospital pharmacists are under pressure to fill prescriptions even during drug shortages, forcing them to buy from gray market vendors at up to 10 times the standard prices for some drugs, including anesthetics and cancer drugs (Aleccia, 2011; ISMP, 2011). More than half of surveyed hospitals in the United States buy cancer medicines from the gray market (Gatesman and Smith, 2011). A similar proportion of U.S. hospital pharmacists and drug buyers report daily inquiries from gray market pharmaceutical salesmen about their inventories (ISMP, 2011). One survey respondent told the Institute for Safe Medication Practices, an NGO, "You are hesitant to tell gray market vendors what you need because they will buy it all up if they find it, and then harass you [to buy it] for months afterwards" (ISMP, 2011). Box 5-2 describes one such gray market purchase.

Some changes to the drugs wholesale system could protect the American consumer. One option would be requiring all organizations that sell wholesale medicines to hold National Association of Boards of Pharmacy (NABP) accreditation. The NABP wholesale accreditation process reviews wholesalers' record keeping, licensing, and drug verification procedures (NABP, 2012a). Accreditation also involves criminal background checks on the most senior operations, buying, and inventory staff, their supervisors, and anyone owning greater than 10 percent interest in the company if it is not publically held (NABP, 2012a). Indiana, North Dakota, and Wyoming require NABP accreditation for wholesalers; wholesalers in other states may voluntarily seek out certification as evidence of their standards (Cherici et al., 2011).

Direct-to-pharmacy distribution is another alternative to the current

BOX 5-2
Falsified Avastin's Circuitous Path to the United States

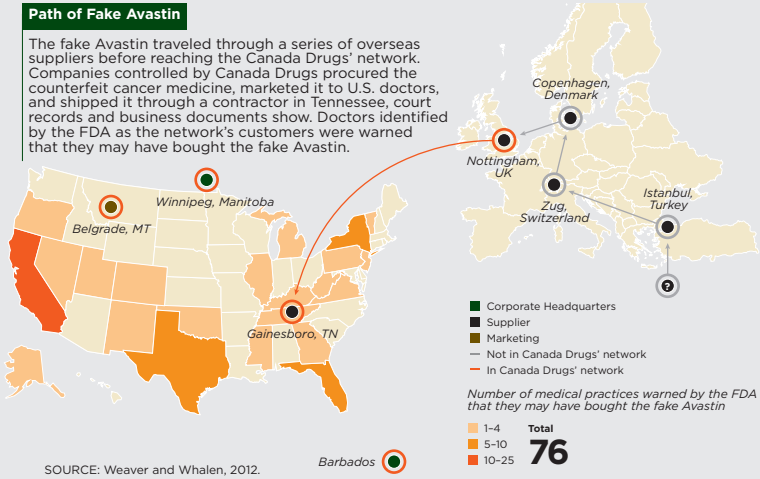
A fake drug originally manufactured in Turkey took a winding path to the United States in late 2011 and early 2012, where it found its way to several physicians' offices. The drug, Avastin, is manufactured by Roche Holding AG of Switzerland and is often used alongside chemotherapy to treat certain lung, colon, and kidney cancers (Faucon and Whalen, 2012). The fake batches contained salt, starch, and various chemicals, but no active ingredients (Blair, 2012). In February and March 2012, the FDA warned approximately 20 practices that they may have received fake Avastin. Later that spring, they expanded the number to 76 potentially affected practices in 22 U.S. states (Weaver and Whalen, 2012) .

The precise origins of the drugs are unknown, as the Turkish company listed on relevant paperwork was not registered with the Turkish authorities, and a trip to its stated address led investigators to a textiles warehouse (Faucon and Whalen, 2012). A Swiss drug distributor, apparently unaware of the problem, purchased the Avastin from Turkey from a Syrian middleman in Egypt, and subsequently sold it to another distributor in Copenhagen (Faucon and Whalen, 2012). From there, the drugs traveled through several companies in Britain and the United States under the parent company Canada Drugs, which operates an online pharmacy that often uses overseas companies to source discount drugs. Ultimately, two U.S. companies sold the drug directly to physicians (Weaver and Whalen, 2012). The high cost of such drugs, at times exacerbated by shortages, may tempt physicians to seek out alternative suppliers to lower their own and their patients' costs and assure a steady supply. At a price several hundred dollars lower per vial than the standard, the falsified Avastin was a good deal for such practices (Weaver and Whalen,

wholesale systems. In this system, manufacturers eliminate secondary wholesalers and use logistics companies to ship directly to the vendor. It has been used, with varying success, in Europe and Australia (Galve and Campos, 2011; Kanavos et al., 2011; Taylor, 2011). There is some concern, however, that direct distribution drives up medicines costs (Exel, 2003; OFT, 2007). It also puts impractical storage and warehousing demands on retailers (Exel, 2003). If direct-to-pharmacy distribution replaces wholesalers with an equally porous network of transport and logistics companies, then it is no improvement.

More rigorous licensing and regulation of the wholesale market, especially the secondary wholesalers, is another solution. The committee believes the secondary wholesale market is the weakest link in the U.S. drug distribution system. Improvements to the secondary wholesale system could

2012). The same forces that lead patients to buy unreliable drugs can lead doctors to do the same, creating yet another vulnerable link in the medicines supply chain.



reduce the number of transactions in the drug distribution chain, thereby improving security.

Recommendation 5-1: State licensing boards should only license wholesalers and distributors that meet the National Association of Boards of Pharmacy accreditation standards. The U.S. Food and Drug Administration, in collaboration with state licensing boards, should establish a public database to share information on suspended and revoked wholesale licenses.

The committee finds that peculiarities of the American wholesale system account for much of the United States' vulnerability to falsified and substandard drugs. Limiting the wholesale market to vetted firms would

make the drug distribution chain less permeable to criminals (Donaldson, 2010). Similar weaknesses plague the wholesale system in developing countries, and action in the American market might give regulators around the world an example and encouragement to tighten controls on the chaotic wholesale and distribution systems.

This recommendation should be implemented in phases over the next 2 years. Collaboration between state licensing boards and the FDA should happen first. Next, the regulators should design the database and publish the processes for collecting accurate, reliable, and timely information about the suspension or revocation of wholesale licenses.

The U.S. Wholesale Market

In the United States, state governments control professional practice, including the practice of pharmacy, which includes medicine distribution and wholesale. Some states have enacted tighter regulations on the market, with unintended spillover effects (Laven, 2006). After the state of Nevada increased oversight of drug wholesale, for example, "some wholesalers simply moved operations across the state line into California" (Flaherty and Gaul, 2003). When unscrupulous businesses can seek out the softest regulatory systems to work in, they do. As the previous section explains, the wholesale trade depends on buying and selling medicines in response to shortages and gluts in different parts of the country. Therefore, the weaknesses in one state licensing system can become vulnerabilities for the others. The committee recognizes the authority of states to license wholesalers but believes that public health will be best protected if all businesses adhere to the strict standards laid out by the National Association of Boards of Pharmacy accreditation process.

Every state has an interest in promoting high minimum standards for medicine sale and manufacture. The recent fungal meningitis outbreak from an steroid injection compounded under unhygienic conditions at New England Compounding Center in September 2012 is a reminder of the risks of competing state standards (Grady et al., 2012; Tavernise and Pollack, 2012). The outbreak and associated infections, which as of January 2013 had killed 45 patients and sickened 693 others in 19 states, was driven by the interstate sale of a compounded steroid (CDC, 2013). Compounding pharmacies are not held to the same standards as big pharmaceutical manufacturers; courts have questioned the FDA's authority over them (Grady et al., 2012). As in the wholesale market, states regulate these businesses in isolation. Though the Massachusetts Department of Health registered three complaints against New England Compounding Center, there is no mandatory national system for sharing these complaints (Grady et al., 2012).

Similarly, there is no way for state authorities to share information on

criminal or negligent wholesalers. As part of a stronger wholesale system, states should report violations and revocations of wholesale licenses to a national, public database. This will impede unscrupulous wholesalers from moving from state to state and starting over when caught in violation of one state's rules. The FDA should facilitate the sharing of this information among states and with the public. The recent tragic meningitis outbreak has brought to light the importance of sharing information on dangerous actors in the drug distribution chain. Although the states have the authority to license wholesalers, the nation's interests are best served by enabling communication among the states.

The Wholesale Market in Low- and Middle-Income Countries

As the previous section explains, the wholesale market is a common vulnerability in medicines distribution around the world. One potential positive outcome of raising the standards for U.S. wholesalers is that it would build international momentum for a leaner, more organized wholesale drug market. Other countries are already working toward more controlled drug wholesale. For example, in 2004 the Chinese drug regulatory authority cut the number of drug wholesalers in the country from 16,000 to 7,445 (Yadav et al., 2011). This is still many more than in the United States, Europe, or Japan, but it is an admirable move in a more sustainable direction.

Proponents of the current drug wholesale system maintain that a small number of wholesalers cannot serve the drugs market of developing countries. They reason that a system of three or four large primary wholesalers may work in Europe or North America, but in developing countries a few companies could never guarantee fine-mesh distribution (Foundation Strategy Group, 2005; McCabe, 2009). Medicine shops in Kenya, for example, report buying from a range of pharmaceutical and general wholesalers both in and outside of the shop's district, as well as mobile vendors and manufacturers (Amin and Snow, 2005).

Others argue that raising the quality standards for drug distribution carries an inherent trade-off of decreased access to medicine (OFT, 2007). Analysis of successful distribution chains, such as the Coca-Cola distribution chain, suggests this is a false dichotomy, however (Yadav et al., 2013). ColaLife, a nonprofit, has been using Coca-Cola's fine-mesh distribution chain to bring oral rehydration and zinc supplements to remote areas since 2008 (ColaLife, 2012). Steps toward a more controlled and efficient wholesale market can protect patients in the markets most hurt by bad-quality drugs. A reduction in the number of licensed wholesalers and use of more efficient distribution chains can help the wholesale market around the world.

DRUG DIVERSION

More stringent licensing requirements can improve the wholesale system, but drugs will still need to move from the factory to the vendor, passing through many hands before reaching the patient. With every transaction on the chain, there is a risk of the drug supply's being compromised. Criminals take advantage of places where the distribution chain breaks down and medicines depart from documented chain of custody. Drugs that leave the proper distribution system are called diverted drugs; the markets that trade diverted drugs, or more generally, markets that trade with little authorized oversight, are called gray markets.

Drug diversion is the means through which medicines approved for sale in one country are sold in others, where they may not be registered. These schemes depend on false statements, forged customs declarations, or smuggling (PSI data shared with the committee, Thomas Kubic, PSI-Inc., July 11, 2012). On the surface, drug diversion is not the public health threat that falsified and substandard medicines are (Bate, 2012). Some countries have made legal provisions for importation of unregistered lifesaving drugs that are not available in local markets (Zaza, 2012). Others argue that thieves bring good-quality drugs to otherwise neglected markets, and that, issues of fraud aside, the end consumer is no worse off (Bate et al., 2010a). If thieves trafficked solely in quality-assured medicines, then this point might be valid. Once a medicine leaves the responsible chain of custody, there is no way to ensure that it has been properly stored. As Chapter 3 explains, drug quality research indicates that unregistered medicines are sometimes dangerous (Bate et al., 2010b; Lon et al., 2006; Stanton et al., 2012; Wondemagegnehu, 1999). By chance, drug diversion may bring good

Key Findings and Conclusions

- When stolen drugs are reintroduced to the legitimate supply chain, there are no records of the products' handling or storage conditions. Diverted drugs are often sold abroad and are of dubious quality.
- A drug pedigree is a record of the drugs' chain of custody. Pedigree requirements prevent stolen drugs from entering the legitimate markets and facilitate efficient recalls.
- There are many methods to create a drug pedigree; all depend on unique serial numbers on the primary pack label.
- A reliable system for tracking and tracing drugs through the distribution chain would reduce the likelihood of illegitimate medicines reaching patients.

products to some patients, but it hurts many more, not only by defrauding the official channels.

Drug diversion is roughly synonymous with theft, and trade in diverted drugs is an indicator of the relative ease with which criminals exploit weaknesses on the distribution chain. Figure 5-3 shows common diversion points in the distribution chain. In the United States, for example, the resale of prescription drugs is a common problem, but illicit vendors also circumvent the regulated distribution chain at other points. In developing countries, the sale of donated drugs for profit is a common type of diversion (World Bank, 2005). Small-scale theft, also called pilfering, happens mostly between the vendor and patients; larger cargo heists tend to happen to bulk drug packages, generally between the manufacturer and the vendor.

Pilfering and Heists

Many diverted drugs are donated ones, pilfered and resold by health workers (Ferrinho et al., 2004; Vian, 2008). The theft and resale of free drugs is engrained in the pharmacy and clinical culture in some countries, where it is seen as a professional perk for otherwise underpaid government health workers (Lim et al., 2012). This theft defrauds donors and contributes to drug shortages at legitimate dispensaries (Bate, 2012), thereby encouraging the distal causes of poor-quality drugs.

Medicines can also be stolen in large quantities earlier in the supply chain. In March 2010, $75 million worth of medicines were stolen from an Eli Lilly warehouse in Connecticut (Efrati and Loftus, 2010) and later partially recovered in Florida (Muskal, 2012). Freight Watch International, a supply chain security company, estimates that theft of pharmaceuticals in the United States increased 283 percent between 2006 and 2008 and have remained roughly constant since then (FreightWatch, 2011b). Warehouse heists such as the Lilly theft are relatively difficult to orchestrate; by far the more common route is theft of a loaded trailer (see Table 5-2) (FreightWatch, 2011b). The companies and the FDA issue warnings about batch and lot numbers of stolen products, but warnings are of limited value when some of the stolen goods are either laundered back into the legitimate supply chain or sold abroad (Burnham, 2012).

Cargo theft is not confined to the United States; Freight Watch International sees it as a serious problem in Brazil, Great Britain, India, Mexico, Russia, and South Africa as well (Fischer, 2012; FreightWatch, 2011a). Indeed, cargo security is generally more of a problem in low- and middle-income countries, where poor roads and slow transit times put shipments at risk for a long time, and in politically volatile places (SCMS, 2012). In any case, the goal of the theft is to sell the diverted shipment.

Sometimes diverted drugs in the market are easy to spot. The Global

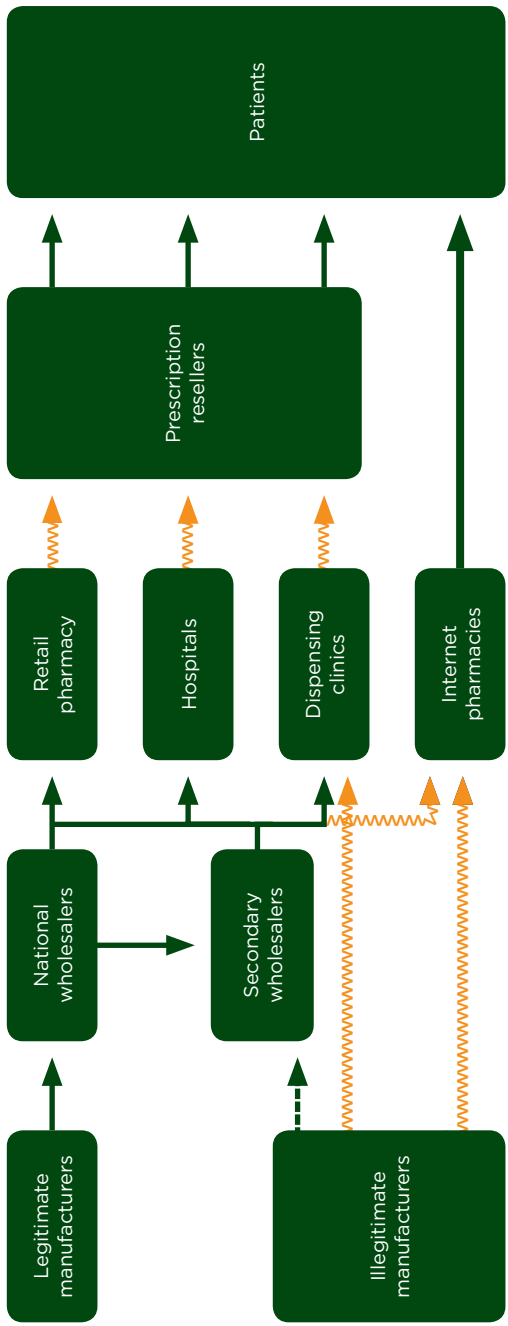


FIGURE 5-3 Risks in the medicine distribution system.

TABLE 5–2 Number of Pharmaceutical Thefts in the United States, 2006-2011

Event Type	Number of Thefts
Theft of a trailer	167
Theft from a trailer	4
Hijacking	12
Facility burglary	9
Facility robbery	1

SOURCE: FreightWatch, 2011b.

Fund finances a line of artemisinin combination therapies for the Affordable Medicine Facility in eight countries, including Nigeria and Ghana (Global Fund, 2012). These drugs are packaged differently from those meant for the public sector (Bate, 2012; Bate et al., 2010a). Roger Bate was therefore able to recognize Global Fund products meant for Nigeria and Ghana in Lomé, Togo (Bate, 2012). Thirty percent of the diverted samples he collected in Togo failed quality tests, a failure his team attributed to degradation (Bate, 2012).

Outward evidence of diversion is not always so clear, but a drug sold in a country where it is not registered is often diverted and therefore suspect. A national sample of essential medicines in Cambodia found that unregistered drugs are six times more likely to be falsified than registered ones (Khan et al., 2011). Similarly, in Ghana, researchers found unregistered oxytocin samples to be uniformly substandard (Stanton et al., 2012). Diverted drugs are dangerous partly because there is no reliable record of what conditions they have been transported in. The uterotonic drugs analyzed in Ghana are unstable at room temperature, for example (Stanton et al., 2012). They might have failed quality testing because of exposure to tropical temperatures and humidity in travel.

Drug Resale and Late Diversion

Drugs can also be diverted late in the distribution chain, after the drug has reached the patient. This is a far less common point of diversion than diversion at the vendor level and earlier. Figure 5-3 refers to this problem as prescription resale. Drug diversion through resale is a growing concern in the United States, where a 2008 survey estimated that between 5 and 10 percent of American high school students take prescription pain killers,

sedatives, tranquilizers, and Ritalin for nonmedical uses (DuPont, 2010). A study of American college students found that more than one-third of those taking a prescription drug had diverted it at some time, but generally this diversion was infrequent sharing among friends, not predictable sales (Garnier et al., 2010).

Other research suggests that Medicaid recipients and other patients sell their medicines for profit in unregulated street markets (Inciardi et al., 2007). Pill brokers may buy medicines from patients, especially elderly ones, or work with unscrupulous doctors to arrange prescriptions for kickbacks (Inciardi et al., 2007). In some ways, drug resale is similar to pilfering as both methods of drug diversion happen in small amounts and attract little attention from the authorities.

Small thefts and large diversions compromise the integrity of the drug distribution chain and confidence in the quality of medicines. In rich and poor countries alike, drugs often circulate outside of the main distribution channels without a drug pedigree, a record of "each prior sale, purchase, or trade of a drug, including the date of those transactions and the names and addresses of all parties to them" (FDA, 2011a). Between the factory and the patient, drugs change hands many times. A drug pedigree controls diversion and gray market sales by preventing a stolen product from coming back into commerce and by recording every merchant who handles the product, thereby deterring prospective thieves.

Tracking and Tracing Products Through the Supply Chain

A strong chain of custody through the drug distribution system can reduce the risks introduced with product diversion and porous supply chains. Track-and-trace systems allow all interested parties to know where the product is at any time and see a record of where it has been previously (Altunkan et al., 2012). These systems allow manufacturers and others to track their products, meaning to follow drugs forward in the distribution chain. They also allow patients or pharmacists to trace the drug, or to verify its past locations.

Track-and-trace systems rely on serialization, the assigning of unique identifying numbers to products. Products that lack identification numbers, or products with identification numbers that cannot be accounted for throughout the distribution chain, must be treated as falsified and removed from the market, even if they come from licensed manufacturers (Altunkan et al., 2012). The unique identifier may be stored in a barcode, electronic product code, or radio frequency chip, or it may be a long-digit serial number.

Barcodes

Mass-produced items such as packaged foods and electronics use machine-readable barcodes to store product information. Some countries require the pharmaceutical industry to mark drugs with unique product codes that contain the product's tracking and identification number. The FDA, for example, requires all human drugs to carry a 10-digit universal identifier called a national drug code (FDA, 2012b). The first digits of the number identify the firm that manufactures, repackages, or relabels the product; the second segment identifies the product, its dosage form, and formulation, and the last digits identify the packaging (FDA, 2012b). The use of national drug codes predated the widespread use of electronic readers (HIMSS, 2003; Simonaitis and McDonald, 2009). In 2004 the FDA issued a rule requiring some human drugs and biologics to carry the national drug code in a linear barcode (FDA, 2011b).[1]

Machine-readable barcodes have many advantages. When used in the hospital or at the point of dispensing medication, these codes can verify that the drug is of the correct dose and dosage form (Pedersen et al., 2003). There is a limit to how much data a simple linear barcode can hold, however. Two-dimensional barcodes can encode more information in a small space and are therefore gaining popularity for supply chain management (McCathie and Michael, 2005).

Two-dimensional barcodes Two-dimensional barcodes, also called matrix barcodes, carry a product serial number, expiration date, batch code, and other information, and they are compatible with older barcode technologies (Lefebvre et al., 2011). Any camera, or even a smartphone, can read a matrix barcode (Altunkan et al., 2012). The camera has to be within the line of sight of the barcode to read it, however, so technicians scan them slowly and one at a time.

Matrix barcodes are printed onto primary packages, and the manufacturer keeps track of the code in a corporate database (Barlas, 2011a). The unique serial numbers carried in the barcode can be downloaded into a regulatory agency database accessible to pharmacists and medicine vendors (Barlas, 2011a). When intermediaries scan the matrix, they record the product's transfers in the database. Information in the barcode should link the bulk and primary packaging. When it fails to do so, much time is wasted in packing, scanning, and repacking shipments (Davison, 2011).

In 2011 the Turkish drug regulatory authority implemented a mandatory pharmaceutical track-and-trace system using two-dimensional bar-

[1] Bar Code Label Requirement for Human Drug Products and Biological Products, 69 *Fed. Reg.* 9120 (Feb. 26, 2004).

codes (Barlas, 2011b). Multinational pharmaceutical companies are obliged to provide two-dimensional barcodes for all products bound for Turkey, though some may print serial labels separately and attach them to packages in-country (Taylor, 2010). The logistics company DHL manages the Turkish labels for some companies (Taylor, 2010). Brazil has a similar requirement, rolled out over 3 years starting in 2009 and allowing a 1-year grace period to sell all warehoused products that predated the requirement (Taylor, 2010).

The use of matrix barcodes for tracking and tracing is not foolproof; barcodes can be forged. They are also not helpful when a patient does not receive the manufacturer's packaging. The system also demands active participation from every intermediary on the distribution chain. If a pharmacist fails to scan the barcode, the information it carries is of no use. Nevertheless, electronic track-and-trace can do much to thwart criminals and protect the drug supply. The systems in Brazil and Turkey give vendors and motivated consumers a way to verify the safety of their products, and they allow regulators to better understand where and how frequently products leave the distribution chain.

A data matrix or two-dimensional barcode on a medicine package.
SOURCE: Altunkan et al., 2012, reprinted with permission. © 2012 IEEE.

Electronic Product Codes and Radio Frequency Identification

Electronic product codes are a form of product code stored in radio frequency identification tags about the size of a grain of rice. The radio frequency tag contains an antenna and a chip (EPCglobal, 2007; Wunder and Roach, 2008). The chip holds the product's unique serial number, expiry date, batch code, and information about its previous transactions; the antenna, when activated by the tag reader, conducts radio energy to the chip to send and receive data (Lefebvre et al., 2011; *RFID Journal*, 2012). The technician reading the chip does not need to position the reader within sight of the tag to read it; the signal is sent by radio waves, not sight. The amount of information encoded in electronic product codes and the ease of accessing this information make the system attractive for drug pedigrees (Lefebvre et al., 2011).

Though some see radio frequency identification (also called RFID) as one of the greatest technological achievements of recent times (Bendavid et al., 2007; Srivastava, 2004), others call it disruptive and over-hyped (Bendavid et al., 2007). The technology clearly has innovative potential, but a critical mass of intermediaries on the drug distribution chain need to upgrade their systems for it to be useful (Lefebvre et al., 2011). Consumer electronics and other expensive products are commonly labeled with radio frequency tags, but using the technology for medicines presents obstacles.

Radio frequency tags are expensive. A 2008 estimate put the cost at $0.11 per tag when bought in lots of 1 million (Wunder and Roach, 2008). After marking each primary package (the smallest unit of packaging) with a radio frequency tag, access to the electronic product code database necessary to decipher the information in the chip costs about $50,000 in the first year (Wunder and Roach, 2008). RFID infrastructure can cost a medium-sized hospital between $200,000 and $600,000 (Yao et al., 2010). The high costs led the U.S. Generic Pharmaceutical Association to call unique serialization "prohibitively expensive" (GPhA, 2012).

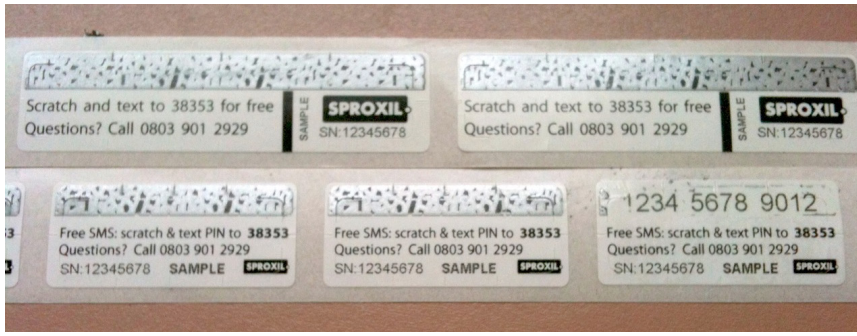
Generics companies in many parts of the world share this sentiment, although the generics industry is not at consensus on the question (Barlas, 2005; Jagdale, 2010; Wolinsky, 2006). Even if the technology were cheaper, it is unclear that it would be practical in the markets most hurt by falsified drugs. Chapter 3 explains that the burden of falsified medicines is borne mostly by the poor, especially the poor in low- and middle-income countries, who buy drugs at unlicensed drug stores and unregulated street markets. As a packaging expert explained to *Express Pharma*, an Indian trade publication, "If you imagine a rural town or village in India—are we really talking sense when we expect an RFID scanner at the outlet?" (Jagdale, 2010).

Mobile Verification

For the time being, the poorest countries are not likely to use electronic tracking systems below the tertiary or bulk packaging at the warehouse level. Mobile phone verification, an ingenious form of mass serialization, can fill in for an electronic pedigree at a drug's last step to the consumer. Mobile verification companies such as Sproxil take subscriptions from drug companies and wholesalers. Sproxil provides labels to their clients; each label is marked with a visible serial number and secret code hidden under the scratch-off surface. When the label is attached to the final package, the manufacturer enters the visible serial number in the Sproxil database through a secure web portal. The visible serial number links the product manufacturer, batch number, manufacture, and expiry dates to the secret scratch-off code.

At the point of purchase, the consumer sends a text message or, in some systems, an e-mail to the verification company, the company that makes the scratch-off labels and manages the linked database. The message is sent to a secure server, usually for no charge. An immediate text message response confirms if the secret code number is registered with the manufacturer, or if it is from a shipment reported to have left the legitimate supply chain. Mobile verification of pharmaceuticals is gaining users in 17 sub-Saharan African countries and India (Mukherjee, 2012; Sproxil, 2012; Versel, 2012). An elegant system for assigning unique product numbers, mobile verification empowers consumers to act for their own safety.

Mobile verification cannot prevent fraud, nor is it a substitute for pharmacovigilance and postmarket surveillance. A product could be substandard at the factory but still gain a valid mobile verification label. Mobile verification, however, appeals to good-quality manufacturers, who see the service as an investment in their brand or as a way for consumers to have



Sproxil standard labels with visible serial number and scratch-off covering the secret code number.
SOURCE: Ashifi Gogo.

confidence in the quality their internal records already show. A more likely problem would be a wholesaler assigning a legitimate label to a falsified drug. Also, the verification service only confirms a product's identity at the end of the distribution chain, at purchase. These systems cannot track the chain of custody or monitor if the product has been stored and transported properly.

A reliable system for tracking and tracing drugs through the distribution chain would greatly reduce the likelihood of falsified and substandard medicines reaching patients. Recent technological advances, such as the use of radio frequency identification and the expansion of mobile phones in developing countries, hold promise for supply chain security. The committee believes that manufacturers and governments should use these technologies to integrate all records of a drug's chain of custody.

Recommendation 5-2: Congress should authorize and fund the U.S. Food and Drug Administration (FDA) to establish a mandatory track-and-trace system. In the interim, the FDA should convene a working group of stakeholders, including the International Federation of Pharmaceutical Manufacturers and Associations and the Generic Pharmaceutical Association, to promote voluntary track-and-trace for all supply chain actors in accordance with existing guidance.

A mandatory track-and-trace system for drugs is the best way to monitor the chain of custody and protect patients from unsafe drugs. A full track-and-trace system would allow all parties in the drug distribution chain to see a complete record of the product's path from the manufacturer to the patient (Rappeport and Jack, 2012). Track-and-trace systems place unique demands on drug manufacturers, retailers, and wholesalers. Some may see the imposition of a drug pedigree system as a matter of pharmacy practice, and therefore under the jurisdiction of state boards of pharmacy, the state health department, or another state authority. To avoid confusion on this question, Congress should clearly authorize the FDA to require manufacturers to trace back finished dosage forms to their constituent ingredients. This authority should accompany an increase in funding to allow the agency, which has received many unfunded mandates in recent years, the staffing and technical upgrades necessary to monitor compliance (McCain, 2011; Palmer, 2010).

A track-and-trace system would allow pharmacists to identify suspicious drugs before dispensing them and would facilitate more efficient product recalls (Buynak, 2011; DeCardenas, 2007). Some versions of track-and-trace exist in the system already. Companies tag drug pallets or other bulk packages with radio frequency tags, for example, but use barcodes or other identifiers on smaller units (Lefebvre et al., 2011). Full track-and-

A child uses a cell phone at a market in Ghana.
SOURCE: © 2006 Joitske Hulsebosch, courtesy of Photoshare.

trace will require changes to drug primary pack labels and changes to the packaging and repackaging practices at wholesale. These changes have delayed acceptance of full track-and-trace (Yukhananov, 2012).

Nevertheless, consumers and governments have demanded a stronger chain of custody (DeCardenas, 2007). This problem has been lingering for years and should be addressed promptly (Palmer, 2012). Without a clear federal mandate on the problem, companies and state governments work in a state of uncertainty, not knowing where and how to make the necessary investments that track-and-trace will require. If Congress does not set a mandatory requirement, then the competing demands of state track-and-trace systems will create an unmanageable burden for manufacturers, wholesalers, and retailers. For example, in 2015 California will require unique serial numbers on pill bottles and drug vials (GPhA, 2011; Norman, 2012).

In 2011, the FDA held a workshop on tracking and tracing prescription drugs. Stakeholder comments on the workshop mentioned the importance of track-and-trace and "the need for one standard, without variations imposed, for example, by individual states" (Ducca, 2011). There is risk to allowing a piecemeal approach to pharmaceutical track-and-trace. Any track-and-trace system will be an expense to manufacturers and industry, but the expense can be contained by making one national requirement.

Other stakeholders commented on the expense of implementing a national track-and-trace system (GPhA, 2011). Generic manufacturers and drug wholesalers operate on lean margins (Berndt and Newhouse, 2010; CBO, 2007). An increased track-and-trace requirement will put a financial burden on these companies, even if the added cost is low. There are also costs to pharmacies, between $84,000 and $110,000, about 0.88 percent of annual sales (*RFID Update*, 2008). Therefore, the committee recommends that the FDA bring all industry stakeholders together to work toward voluntary use of track-and-trace technology. This can help control the burden an inevitable shift to drug tracking will put on these businesses.

Tracking primary packages through the drug distribution chain with unique serial numbers is a good defense against criminal infiltration (Ludwig, 2012; Pellek, 2009; Power, 2008). A method of tracking medicines from the factory to the consumer could greatly reduce the chances of a dangerous product being sold at a reputable pharmacy. These solutions are of limited value in the vast pharmaceutical gray markets, however. Ignorance, convenience, and desperation, or some combination thereof, drive patients to unlicensed pharmacies in street bazaars and on the internet. Medicines retail, the last leg of the drug distribution system, is often the most chaotic.

MEDICINES RETAIL

The drug distribution system becomes more disordered as the products leak out of regulated distribution chains. The risk increases as drugs move farther from the manufacturer en route to the vendor. Licensed pharmacies and dispensaries can control the quality of their stock, at least insomuch as they can trust their wholesalers. There are no such efforts at quality control in the unlicensed market. Unlicensed vendors are often minimally educated. They may approach medicines dispensing as any other sales job and not want a customer to leave without making a purchase. In general, these vendors exploit the chaos inherent to street markets and dry goods shops in low- and middle-income countries and to online drug stores in middle- and high-income ones. Their stock is poor because the stockists are either unable or unwilling to judge quality.

Their customers are similarly ill-equipped to evaluate the dangers of buying medicine outside of controlled chains. Unlicensed medicine vendors fill a need, especially in poor countries, when time, expense, and distance impede access to registered pharmacies. Internet pharmacies can fill a similar void, appealing to customers eager to save time and money or to purchase discretely. Both types of market are dangerous and more similar than they may appear at first glance. A Chinese military pharmacist described the appeal of unlicensed medicine shops: "There are people who choose to seek medical help from these places, possibly because of lower prices or privacy concerns, which may increase their chances of getting counterfeit products" (Quingyun, 2012). The observation is true of all unregulated

Key Findings and Conclusions

- There are few high-quality, licensed drug shops in developing countries, especially outside of cities.
- Drug sellers in developing countries often do not have the training to oversee the purchasing and dispensing of medicines.
- Drug seller accreditation and franchising programs have improved drug retail in some developing countries. Task shifting and vocational training in medicines retail can alleviate the shortage of pharmacists. Government incentives can help keep trained staff in underserved areas.
- Internet pharmacies are often the disorganized drug markets of developed countries. Only 7 percent of countries have a system for verifying legitimate online drug stores.
- In the United States, the expense of drugs contributes to the draw of online drug stores.

pharmacies. Street markets and the internet are a main source of falsified and substandard medicines for patients around the world (WHPA, 2011). The committee believes some changes to medicines retail could improve the world's vast and disorganized pharmaceutical bazaars.

Unregistered Pharmacies in Low- and Middle-Income Countries

The packaging of falsified drugs contains clues that are lost in unregulated pharmacies (Dondorp et al., 2004). Epidemiological research suggests that falsified medicines are often sold without packaging (Basco, 2004), by street vendors (Tipke et al., 2008) or by patent medicine dealers (Onwujekwe et al., 2009). The dangers of these vendors are clear: Some sell loose pills from large plastic bags or cut apart and subdivide blister packs; none has training in the proper storage, buying, or dispensing of medicines. Even when packaged medicines happen into these markets, their customers are not often sophisticated enough to analyze packages for irregularities. Illiteracy is a known predictor of buying falsified and substandard drugs (Erhun et al., 2001), and it is the poorest and least educated patients who buy medicines from unauthorized dealers (Nkamnebe, 2007). As David Peters and Gerald Bloom observed, "The wealthiest people in developing

Medicine for sale in a Côte d'Ivoire street market.
SOURCE: Issouf Sanogo/Getty Images.

nations tend to use highly regulated services. The poor, by contrast, usually seek care elsewhere" (Peters and Bloom, 2012, p. 164).

Shortage of Quality-Assured Drug Shops

A simple lack of alternatives pushes the poorest consumers to buy medicine at unregulated shops. High taxes and overhead costs make a difficult business environment for pharmacists; there are few incentives to work in underserved areas (McCabe, 2009). Research on drug shops in rural Tanzania found that despite gross regulatory violations, including stocking of controlled medicines, selling loose tablets, selling of unregistered drugs, and near universal lack of qualified staff in sales, the shops operated with the government's tacit permission (Goodman et al., 2007).

The regulatory authority might not have enough inspectors to monitor all drug shops on the prescribed timetable (Goodman et al., 2007; MSH, 2012). The Ghanaian Pharmacy Council, for example, inspects only about 20 percent of all drug sellers annually (Segrè and Tran, 2008). Inspectors commonly find the shops selling restricted medicines, the products that bring in about half of the stores' total revenues (Segrè and Tran, 2008). The low likelihood of being caught in a violation and the social and financial incentives to ignore regulations outweigh the threat of punishment for many shopkeepers (Segrè and Tran, 2008). When infrequent inspection does identify violations, regulators are loath to enforce the rules, as this would remove from many communities their only medicine store (Goodman et al., 2007).

These inspectors realize that even unlicensed drug shops serve a purpose in developing countries, especially outside of cities, where there are no licensed pharmacies (MSH, 2012). People in rural areas use these shops for more than just retail; the shopkeepers are a source, sometimes the sole source, of health advice in their communities (Anderson et al., 2009; Azhar et al., 2009; Bustreo et al., 2003; Goel et al., 1996; Peters and Bloom, 2012). The accuracy of the information they give is doubtful, however (McCabe, 2009). In some parts of the world, so-called pharmacy assistants may have less than a middle-school education (Goel et al., 1996). These shopkeepers are not properly trained for medicines retail, let alone patient counseling.

Shortage of Trained Pharmacy Staff

Poor supervision of medicines retail allows falsified and substandard products to circulate. Pharmacists oversee the responsible purchase of drugs from legitimate wholesalers. They watch for suspicious products in the licit supply chain, educate patients on warning signs of problem drugs, and are

the first line of postmarketing surveillance (Ziance, 2008). Too few people are trained to do this job in the parts of the world where falsified and substandard medicines are a systemic problem. As Figure 5-4 shows, poorer countries often have more pharmacies than pharmacists, sometimes many times more; in some counties even these estimates may be inflated (FIP, 2009). The International Pharmaceutical Federation (known by the French acronym FIP) estimates that only slightly more than half of all pharmacists are active in the workforce (FIP, 2009).

The WHO commented on this problem in a 2010 report, observing that many types of medicines outlets in sub-Saharan Africa are not managed by pharmacists (WHO, 2010). In general, the region has a pharmacist for every 23,375 people; 75 percent of these pharmacists live in Nigeria or South Africa (Kome and Fieno, 2006). After excluding these countries, the ratio is closer to 1:64,640 (Kome and Fieno, 2006). Though the shortage is especially acute in sub-Saharan Africa, the ratio of pharmacists to population in most low- and middle-income countries falls far short of the WHO-recommended 1:2,000 (Azhar et al., 2009). National estimates in Malaysia (1:6,207) and Pakistan (≈ 1:19,748) also suggest serious problems (Azhar et al., 2009).

The world distribution of pharmacists shown in Figure 5-5 indicates a dearth of pharmacy professionals in sub-Saharan Africa and Southeast Asia. This map fails to capture the relative privation of rural areas, where far fewer pharmacists per person work (Hawthorne and Anderson, 2009). In India, for example, most pharmacists work in the country's drug manufacturing sector (Mohanta et al., 2001). So, although the national average ratio of pharmacists to population is 1:1,785, this number masks regional disparities (Basak et al., 2009). In states with less manufacturing the ratio hovers around 1:4,000 (Basak et al., 2009). All states struggle with a pronounced rural-urban imbalance. Few pharmacists work outside of cities, and almost none works in remote areas (Basak et al., 2009). This problem is not unique to India. Survey data indicate that managers around the world find it difficult to fill pharmacy positions in the public sector and outside of urban areas (FIP, 2006).

Rural disadvantage starts with education. Pharmacy schools are in cities and therefore attract urban students who have little interest in working in the countryside or reason to move there after graduation (Anderson et al., 2009). Furthermore, pharmacy training in many low- and middle-income countries, especially in Asia, qualifies people to work in industry (Azhar et al., 2009; Mohanta et al., 2001). A critic of the Indian pharmacy education system observed, "Community pharmacy practice does not exist in its true sense, only drug selling" (Mohanta et al., 2001, p. 810).

Improvements to the practice of community pharmacy would curtail

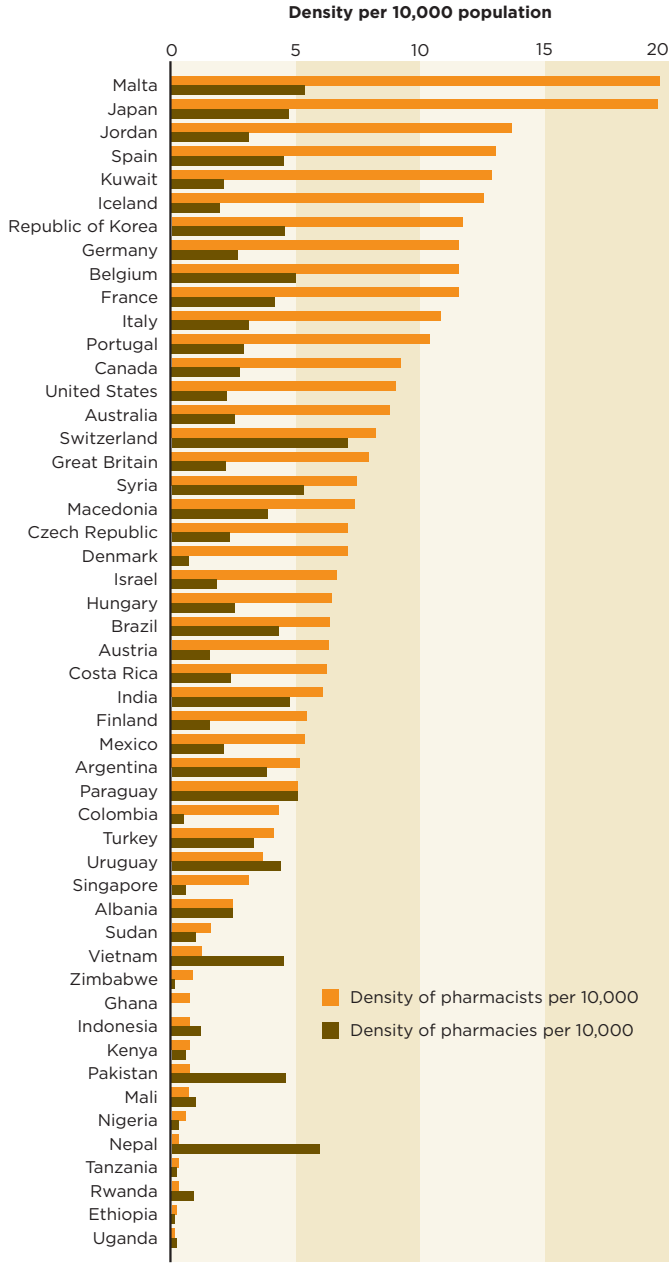


FIGURE 5–4 Number of pharmacists per 10,000 people and number of pharmacies per 10,000 people in 50 countries.

SOURCE: FIP, 2009 (http://www.fip.org/pharmacy_education).

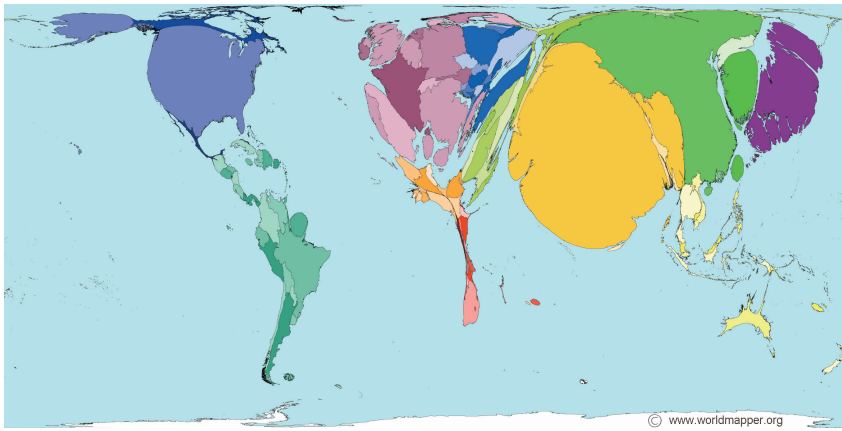


FIGURE 5–5 The world's pharmacists, pharmacy technicians, and pharmacy assistants, 2006 data.

SOURCE: Worldmapper, 2006. © Copyright SASI Group (University of Sheffield) and Mark Newman (University of Michigan).

the sale of poor-quality drugs in low- and middle-income countries. However, having practicing community pharmacists oversee all pharmacies is an unrealistic solution in the parts of the world most hurt by falsified and substandard pharmaceuticals. Viable short-term solutions should aim to increase the reach of legal drug shops staffed by sellers with appropriate minimal training. The committee believes that governments and the private sector both have important roles in assuring a safe medicine supply in underserved areas.

Recommendation 5-3: Governments in low- and middle-income countries should provide an environment conducive to the private sector establishing high-quality medicines retail in underserved areas. Government incentives could encourage this. To the same end, governments, the World Health Organization, and the International Pharmaceutical Federation should support national pharmacy councils and education departments to train tiers of pharmaceutical personnel.

The committee recognizes two main problems with medicines retail in low- and middle-income countries. First, there are not enough high-quality vendors, driving customers to street markets and unlicensed shops. Second, there are not enough trained staff to oversee the responsible purchasing and

dispensing of medicines. This is a problem in both rural areas and slums (Azhar et al., 2009; Riley et al., 2007).

The committee recognizes that supplying cheap, quality-assured drugs to the population is not a realistic goal for many governments, especially in poor countries. These countries can encourage private-sector investment in medicines and facilitate task shifting among pharmaceutical staff, however. Examples of successful programs that improved medicines access follow.

Improving Retail

Providing safe, affordable medicine to the population is not within the budget of many countries. The private sector, however, will invest in medicines retail if there is a good business reason to do so. Governments can take steps that would encourage private-sector investment and create an environment where responsible private drug sellers will thrive.

One promising example of government and private-sector investment in medicine retail is the Accredited Drug Dispensing Outlet (ADDO) program in Tanzania (MSH, 2012). The Tanzanian regulatory authority was eager to discourage illegal stocking and improve dispensing practices at unregistered drug stores through an accreditation program (MSH, 2012; Rutta et al., 2011). The Bill & Melinda Gates Foundation funded the program, which used a combination of training, incentives, and creation of consumer demand to drive changes in the private sector (MSH, 2005; Rutta et al., 2011). Trainers from the Tanzanian Ministry of Health educated drug shopkeepers on proper dispensing techniques, medicines storage, national regulations, business skills, and ethics (MSH, 2005; Rutta et al., 2011). The government offered low-interest loans for improving drug shops, many of which had been stuffy, hot, humid (therefore unsuitable for medicine storage), and not properly secured against theft (MSH, 2012). Participants who met the program's standards were rewarded with legal authority to sell some controlled drugs (MSH, 2005). The government has made efforts to increase the ADDO customer base, allowing ADDOs in some districts to dispense subsidized artemisinin combination therapies (Rutta et al., 2011). The subsidy also ensures that good-quality antimalarials are as affordable to poor customers as the ubiquitous falsified ones.

The ADDO certification program conferred a competitive advantage on participating shopkeepers. A widespread social marketing campaign on access to malaria drugs promoted the outlets as reliable vendors (Hetzel et al., 2007). This publicity helps build consumer confidence in the program and create demand for the outlet's services. An emphasis on customer service and good management in the accreditation process gave the shops a professional quality that enhanced consumer satisfaction.

Franchising is another private-sector approach to improving drug retail. The Ghanaian Social Marketing Foundation, a national NGO, founded the CareShop franchising program to improve access to good-quality medicines in Ghana (Segrè and Tran, 2008). The foundation recruited franchisees from among licensed chemical sellers, attracting them with an improved supply chain. The drug sellers had been spending an average of 30 percent of their time purchasing from an unreliable wholesale market (Segrè and Tran, 2008). The franchiser guaranteed supply and direct delivery of the shop's entire inventory, thereby saving the shopkeeper time and about $227 per year in travel expenses (Segrè and Tran, 2008). This system also puts wholesale buying in the hands of a purchaser qualified to judge product quality. The purchaser's frequent large orders command a collective buying power that controls costs.

Customer loyalty to the CareShop franchise grew quickly in the program's first 4 years (Segrè and Tran, 2008). With 270 outlets, CareShop is one of the largest drug store franchises in Africa (Segrè and Tran, 2008). Box 5-3 present profiles of two typical CareShop franchisees.

Drug seller accreditation improves medicine quality at the place most patients will, from convenience and habit, turn to first (MSH, 2012). In Kenya, the United States Agency for International Development funded a public–private drug seller accreditation program that increased the rational dispensing of antimalarials among participating shopkeepers (MSH, 2012; Tavrow et al., 2002). Drug seller accreditation requires making the best use of the shopkeepers already selling medicines. Part of the project's success came from its training of motivated drug shopkeepers.

Pharmaceutical Task Shifting

Training and credentialing of drug shop staff must accompany any successful accreditation program. Task shifting, delegating responsibilities from doctors, nurses, and pharmacists to less specialized lay health workers, is a way to improve the shortage of health professionals in developing countries (Fulton et al., 2011; WHO, 2008). There is international support for task shifting in pharmacy, especially in the training of pharmacy technicians, which is often a kind of post–high school vocational training in dispensing medicines (Bureau of Labor Statistics, 2012; Hawthorne and Anderson, 2009).

International organizations such as the FIP and the WHO cannot dictate the best training programs and levels of pharmacy staff needed in hundreds of different countries (Anderson et al., 2009). They can, however, help ministries of education and national pharmacy councils identify the competencies a vocational pharmacy worker would need in their country. Their efforts in-country should aim to identify the competencies and

BOX 5-3
CareShop Franchisee Profiles

Rose Kaade Apreku

"Upon the completion of primary school, Ms. Apreku worked on her family farm prior to saving enough money to start her own licensed chemical shop. She estimates that it cost $300 to open her shop. Ms. Apreku explained that the CareShop franchise drastically improved her business in several ways. First, she is able to advise her customers more confidently on the nature and appropriate treatment of their afflictions. Second, she is able to offer her patients better customer service through complementary selling techniques. Lastly, she is able to track her sales and pricing using a ledger. Ms. Apreku's sales are five times higher than they were prior to conversion, and she runs the store from 7 am to 10 pm every day with the help of Adams, her son (also pictured)" (Segrè and Tran, 2008, p. 31).

Kofi Asiam

"Mr. Asiam inherited his chemical shop, a converted space attached to his home, from his father and was a licensed chemical seller for nearly 20 years prior to his conversion to CareShop. Commenting on the difference between his business before and after conversion, Mr. Asiam notes, 'It is a tremendous difference. CareShop has enlightened us. Our customers now see our place as a beautiful place.' During his renovation process, Mr. Asiam spent roughly $200 on improvements, which include ceiling fans, a refrigerator, and glass display cases. These are important differentiators because Mr. Asiam has four competing LCS [licensed chemical sellers] within a kilometer of his own shop" (Segrè and Tran, 2008, p. 31).

minimum training necessary to work in medicines retail. They might also consider developing chains of supervision wherein minimally educated staff manage stock and then report their needs up to someone who is qualified to identify good-quality wholesalers and buy from them. The committee believes that national pharmacy councils are best able to articulate what the proper reporting chain should be in their country and what minimum qualifications their countries' patients will accept. The minimum training for a drug dispenser or pharmacy technician in rural Canada will be different from what is suitable to rural Nepal. In any case, there should be emphasis on vocational training to credential medicine shopkeepers and include them in the health system.

There is evidence that task shifting can alleviate the pharmacist shortage in developing countries. In Malawi, an emergency training and credentialing program for health workers increased the number of pharmacy technicians by 84 percent between 2004 and 2009 (O'Neil et al., 2010). Malawian pharmacy technicians supervise pharmacy attendants, the lower-level staff who stock and dispense drugs, allowing the technician more time for stock management and other more complicated tasks (Shulman et al., 2009). Because of task shifting, pharmacy technicians monitor adherence to antiretroviral treatment in Zambia and tuberculosis treatment in urban Uganda (Bolton-Moore et al., 2007; Mafigiri et al., 2011; Stringer et al., 2006).

Training and task shifting programs that recruit minimally educated shopkeepers are also promising. For example, Kilifi, Kenya, is a rural area of 70,000 people with 15 licensed dispensaries and pharmacies and 316 general stores that sell medicine (Marsh et al., 2004). A training program for Kilifi shopkeepers more than doubled the proportion of antimalarials sold in adequate dosage (Marsh et al., 2004). A similar Kenyan program trained mobile wholesalers or wholesaler counter attendants to teach drug retailers about correct malaria drug dosing (Tavrow and Shabahang, 2002). After 6 months, mystery shoppers were nine times more likely to receive the correct drugs in the correct dose from retailers who had participated in the program (Tavrow and Shabahang, 2002).

Giving Incentives to Pharmaceutical Personnel

Using workers more efficiently could do much to remedy chaotic drug retail in low- and middle-income countries, but there is also a problem of retaining trained staff in underserved posts. Even minimal technical training confers a competitive advantage in the labor market, especially in poor countries (Attanasio et al., 2009; GTZ, n.d.; Kasipar et al., 2009). Newly minted pharmacy technicians or drug dispensers can easily leave their rural

assignment for better paying jobs in places with a higher standard of living and better opportunities for their children. This pattern can undermine the best efforts to improve rural-urban equity and should be discouraged, while respecting the individual right to emigrate.

Governments should reward service in underserved areas and attempt to mitigate the hardships of these posts. The people who take advantage of training programs are bright and ambitious. They naturally want their children to be at least as educated as they are. Scholarships for the children of pharmacy staff in underserved areas could assuage fears that a rural posting puts their children at a disadvantage. Efforts to guarantee good schooling for children, possibly through boarding schools or scholarships, could remove a barrier to rural service (Rao et al., 2010). Better salaries can draw trained staff to cities, but tax breaks and hardship pay can alleviate this obstacle (CSG, 2008; Rao et al., 2010).

Health workers also have concerns about quality of life and physical hardships in rural posts (Rao et al., 2010). Subsidized housing or provision of modern living quarters could help in places where this is a common concern. It is also possible to recruit pharmacy technicians and pharmacy assistants from underserved communities. Training students from rural and remote areas is a known way to reduce attrition in these posts (Rabinowitz et al., 1999). The Australian Rural and Remote Pharmacy program has successfully increased service to rural and isolated communities, in part through giving scholarships to students from rural backgrounds (see Box 5-4).

Internet Pharmacies in Middle- and High-Income Countries

Disorganized medicines retail is not confined to developing countries. The previous section describes the large gray market for medicines in bazaars and unlicensed drug shops in low- and middle-income countries. The internet serves the same purpose, but mostly in middle- and high-income countries. Illegitimate internet pharmacies are similar to unlicensed drug shops both in the quality of the products they stock, which is poor, and in the lack of official oversight of their operations (Crawford, 2003). And, because the internet facilitates easy international sales, online drug stores have spread the problem of falsified and substandard drugs "from small, unprofitable, markets in developing nations to the [drug] industry's most lucrative markets" (Lybecker, 2007, p. 512).

The Legality of Internet Drugs Retail

A 2011 survey of 114 WHO member states found that the majority of countries had no laws governing the operation of internet pharmacies

BOX 5-4
The Australian Rural Pharmacy Workforce Program

The Australian government began the Rural Pharmacy Workforce Program in 1999 as part of a broader effort to improve rural and indigenous people's health care (Australian Government, 1999). The program aims to improve access to pharmacy services in rural or remote regions and includes a variety of initiatives to improve recruitment and retention of rural pharmacists.

One part of recruitment is raising awareness of rural pharmacy as an attractive career choice (KPMG, 2010). Recruitment materials emphasize the benefits of a rural career, including increased patient interaction, diverse career paths, a more laid-back lifestyle, close-knit community life, altruism, and excitement (PGA, 2011). A 2009 DVD campaign promotes the same messages to high school students (KPMG, 2010).

The program also increases pharmacy students' exposure to rural work during their training. Australian pharmacy students work in community or hospital pharmacies as part of their studies. Most will do so in an urban area (PGA, 2012b). By paying housing and transportation costs, the program allows universities to place students in rural internships (PGA, 2012b). Positive internship experiences encourage students to practice in rural areas during their careers (FIP, 2009).

The program also supports students from rural backgrounds to pursue pharmacy degrees. Rural students are twice as likely to return to rural areas after graduation as students from cities (FIP, 2009). The Rural Pharmacy Scholarship Scheme awards rural students $10,000 per year of study and pairs them with a mentor who also works in rural pharmacy (PGA, 2012a).

Professional isolation can lower retention of rural pharmacists (KPMG, 2010). A continuing education program aims to avoid this pitfall by funding rural pharmacists' professional development (KPMG, 2010). Another successful initiative to improve retention is the program's emergency locum service. This offers rural pharmacists direct, 24-hour access to replacement pharmacists in emergency situations when they need to leave their practices (KPMG, 2010). The service ensures that rural pharmacies remain open and that communities have continued pharmacy access (FIP, 2009).

The FIP has praised the Australian program as the world's most comprehensive rural pharmacy improvement (FIP, 2009). An independent evaluation found that both rural pharmacists and consumers valued its initiatives (FIP, 2009). The program is credited with expanding pharmacy service in rural Australia by 13 percent, eight times faster than the national average (FIP, 2009).

(WHO, 2011). Of those countries that have legislation about internet pharmacies, more disallow (19 percent) than allow them (7 percent) (WHO, 2011). Figure 5-6 shows the geographic breakdown of the 30 countries that have legislation on the operation of internet pharmacies.

One of the most common tools for governing internet pharmacy is accreditation and certification, though only 7 percent of responding countries have a national process for certifying, accrediting, or regulating internet pharmacies (WHO, 2011). Most of these countries are in Europe, and all are either in the World Bank's high-income or upper-middle-income groups (WHO, 2011). A few countries have an accreditation process for their own internet pharmacies, but internet commerce is transnational. Legislation on internet pharmacies outside of a country's jurisdiction is even less common; only 25 percent of the 144 countries surveyed have legislation governing the purchase of medicine from foreign countries (WHO, 2011). The countries that allow purchasing from online pharmacies abroad are mostly in Europe (WHO, 2011), where the single market has hastened consideration of trans-

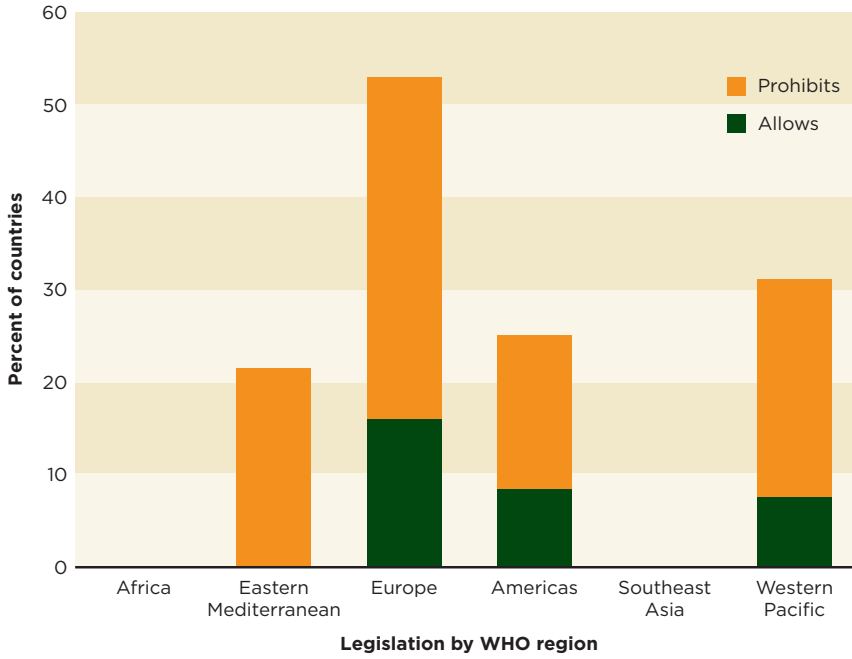


FIGURE 5–6 Legislation of internet pharmacy operations by WHO region.
NOTE: WHO = World Health Organization.
SOURCE: WHO, 2011.

national commerce. Perhaps concern about the practicality of enforcing laws against internet drug sales prevents countries from passing them. It may also seem futile to ask internet drug sellers to observe the same standards registered pharmacies do, such as requiring doctor's prescription for controlled medicines, when "national rules banning the sale of drugs without a prescription can be easily overcome" (Levaggi et al., 2012, p. 245).

Just as often, restrictions and quality controls for online pharmacies are not, in fact, violated because many internet pharmacies operate out of countries that have no such restrictions. Rogue internet pharmacies, those that sell dangerous products and avoid inspections, commonly operate from low- and middle-income countries (Baert and De Spiegeleer, 2010; FDA, 2005). The United Nations Office on Development and Crime (UNODC) reckons India supplies the most drugs for illegal online pharmacies (UNODC, 2010). Although regulatory agencies can ask foreign governments to close online drug stores, it is difficult to prevent them from reopening at a different address (Ivanitskaya et al., 2010). Because the products are sent through courier or postal services, customs and border officers may also stop the imported drugs at the port of entry (Ivanitskaya et al., 2010).

The Attraction of Internet Pharmacies

Some of the more reputable-looking internet drug sellers keep up the pretense of having patients complete a health questionnaire before buying drugs, but many do not (Ivanitskaya et al., 2010; Orizio et al., 2011). Far more variable is the requirement for a doctor's prescription (Orizio et al., 2011). A European study found 62 percent of medicines bought online to be falsified or substandard or both (EAASM, 2008). The U.S. Government Accountability Office found that only about 20 percent of the 21 online pharmacy samples were falsified, though another three samples were possibly degraded (GAO, 2004).

Bostwick and Lineberry proposed four main categories of customers at internet pharmacies: bargain hunters, the poor or elderly, the "lifestyle libertines" who prefer to self-prescribe, and drug addicts (Baert and De Spiegeleer, 2010; Bostwick and Lineberry, 2007). Of these groups, addicts are the least likely to purchase prescription drugs online (Inciardi et al., 2010). Internet drug stores cater to people who like to buy drugs without, or even against, a physician's advice (Levaggi et al., 2012), or to those who cannot otherwise afford their medication (Baert and De Spiegeleer, 2010). Table 5-3 shows other perceived advantages and disadvantages of online pharmacies.

Other online shoppers seem motivated by a belief, sometimes a mistaken one, that internet pharmacies sell cheaper drugs. In a sample of 19

TABLE 5–3 Advantages and Disadvantages of Internet Pharmacies

Advantages of Online Pharmacies	Disadvantages of Online Pharmacies
Available 24 hours per day, 7 days per week	Limited participation by third-party payers
Lessened perceptions of intimidation when obtaining embarrassing or sensitive drugs	Pharmacists not always immediately available online to answer important questions patients may have
Some sites allow patients to check medication profiles online	Concerns about issues of privacy of information
Medications delivered directly to patient's home via standard or special mail	Concerns about security of financial information transmitted
Convenience	Questions about the integrity of drugs shipped
Medication availability to patients with physical or other disabilities that hinder retail patronage	Questions about the quality of drug information provided
	May bypass the pharmacist/patient and physician/patient relationship
	Difficult to ascertain whether licensed practitioners are dispensing drugs or providing consultations

SOURCE: Crawford, 2003.

websites, Levaggi and colleagues found that one-third of their drug orders never arrived, though no company issued refunds (Levaggi et al., 2012). On average, the investigators paid more for the drugs that never arrived than for those that arrived (€0.83 per pill for those that arrived, €1.27 for those that did not). Investigators cited other hidden costs, including shipping and customs fees, as well as the cost of time spent waiting for the slow transactions to process (Levaggi et al., 2012). More importantly, of the 13 pharmacies that filled orders, only two were *not* of substandard quality (Levaggi et al., 2012).

Levaggi and colleagues are an Italian research group. They criticized the false economy of online drug sellers in part because the products they bought sell for less in Italian regulated, storefront pharmacies (Levaggi et al., 2012). For consumers in the United States, the cost-to-benefit analysis is not as clear. A 2001 study of Parkinson's disease medications found online drug stores offered substantial savings off U.S. list prices; brand-name drugs were 7 to 58 percent cheaper, generics 31 to 76 percent less expensive (Wagner et al., 2001). A study of American shoppers at internet pharmacies found that 37.6 percent perceive the costs as one of the main advantages of internet drug sellers (Crawford, 2003).

Some internet pharmacy shoppers choose to bypass the regulated medicine channels out of arrogance or ignorance. Others understand the risks but have no better alternative. A *Forbes* magazine contributor explained, "My wife needs the meds to stave off a recurrence of cancer, so avoiding [online pharmacies] is not an option" (Wasik, 2012). The risks of online purchases are, especially in the United States, inextricable from larger questions of affordable drug pricing (*Financial Times*, 2012). Every year more Americans, and others accustomed to using the internet for bargain shopping, import "incremental amounts" of medicines to their countries though gray market internet purchases (Laven, 2006; Shepherd, 2007b). Many of these patients presumably struggle with the dilemma the UNODC described: "In some cases, cheaper but lesser quality medication is better than nothing; in other cases, it clearly is not" (UNODC, 2010, p. 184).

Distinguishing Rogue Pharmacies from Legitimate Ones

In late September 2012, Interpol, an intergovernmental organization for police cooperation, organized an international raid of online pharmacies

A GlaxoSmithKline ad campaign about the dangers of online pharmacies purporting to sell Canadian medicines.
SOURCE: Lybecker, 2007.

(Interpol, 2012a). The operation, known as Pangea V, is part of Interpol's enforcement against pharmaceutical crime. Regulatory, customs, and law enforcement agencies in 100 other countries took part in the operation, which shut down over 18,000 internet pharmacies and led to 79 arrests (FDA, 2012a; Interpol, 2012b; Shelton, 2012; *TechNewsDaily*, 2012). In the United States, the FDA estimates that Pangea V led to closing of more than 4,100 illegal online drug sellers (FDA, 2012a).

By the agency's own admission however, such efforts are futile. Ilisa Bernstein, acting director of the FDA Center for Drug Evaluation and Research, explained, "We don't know how many websites are out there, but there are a lot more . . . they can pop up days or weeks later using another URL and another way to deceive consumers" (Shelton, 2012). Although there is value to shutting down criminal online drug stores, in the longer term, it may be more helpful to recognize the e-commerce division of legitimate pharmacies.

The challenge of recognizing legitimate online pharmacies As Table 5-3 mentions, online pharmacies can be a boon to people who live in remote areas or who cannot manage in-person shopping. These consumers need reliable advice on how to navigate the confusing internet marketplace. There are many reputable pharmacies with licensed e-commerce divisions, but identifying them can be difficult.

Both the United States and Europe have accreditation programs for legitimate online pharmacies. In the United States, the National Association of Boards of Pharmacy runs the Verified Internet Pharmacy Practice Sites (VIPPS) accreditation program (NABP, 2012b). To earn accreditation, online pharmacies must comply with state licensing requirements for both the state the pharmacy is in and for all the states in which it dispenses medicines (NABP, 2012e). Chief among these requirements are the authentication of prescriptions, observance of quality-assurance standards, and submission to regular state inspections (NABP, 2011, 2012e). Accredited pharmacies are rewarded with the VIPPS seal, but because the seal would be easily copied, the project website lists both certified pharmacies (the good list) and known fraudulent ones (the bad list) (Ivanitskaya et al., 2010; NABP, 2012c,d). Most VIPPS-certified pharmacies are online divisions of national chain drug stores (deKieffer, 2006). The program also recognizes some independent internet businesses such as Medco's Express Scripts (Medco Health, 2012). The certification process is not perfect, however. An online drug store later exposed for dispensing narcotics inappropriately briefly enjoyed VIPPS accreditation (deKieffer, 2006). As of 2012, 30 pharmacies have earned VIPPS accreditation (Bate et al., 2012).

Similarly, the European Medicines Agency (EMA) has made controlling internet sales one of the four pillars of their falsified medicines legislation

Customs and border police inspect packages during Pangea V.
SOURCE: © Carabinieri NAS (Italia).

(Cockburn, 2011). They are planning a consumer education campaign starting in the summer of 2013 that will empower consumers to give their business to a reputable online pharmacies (Cockburn, 2011; EMA, 2011; personal communication, David Cockburn, January 18, 2013). In addition to patient education materials, the agency's website will link patients to national regulatory authorities' websites that will maintain a list of authorized online pharmacies. The authorized pharmacies will in turn post an accreditation logo that links back to the regulatory agencies' website (Cockburn, 2011). The Royal Pharmaceutical Society of Great Britain also has a registration logo that legitimate online pharmacies can display (EAASM, 2008).

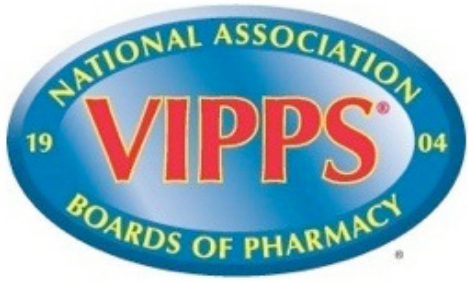
The VIPPS system and its EMA counterpart rely on accreditation from trusted national health organizations. The committee agrees that independent accreditation is a useful tool for consumers trying to make sense of the chaotic world of online medicine retail. Even the accreditation can add to confusion, however. A 2008 study found that about 20 percent of online drug stores displayed an approval of a regulatory or accrediting agency, but about 80 percent of these approvals were phony (Mayor, 2008).

Although there are many good-quality online drug stores, the illicit

ones outnumber them. The American National Association of Boards of Pharmacy found the vast majority (97 percent) of a sample of more than 10,000 online drug sellers they examined to be in violation of pharmacy laws and standards (DrugTopics, 2012). Furthermore, the internet confuses the cues customers might usually use to judge quality. There is no pharmacist to counsel patients on online pharmacy, and a website claiming affiliation with a respected local chain might be lying. A 2005 study found that of the more than 11,000 online drug stores claiming to be Canadian, only 214 were registered with the Canadian authorities (Clabaugh, 2005).

Proponents of online drug stores maintain that consumer demand can keep online sellers to standards by driving the development of "private verification services" (Bate et al., 2012). Research indicates, however, that even patients with a sophisticated understanding of both health and technology are poorly equipped to judge the quality of online drug sellers. Between 2005 and 2008, 1,914 undergraduates completed the e-Health literacy assessment, rating highly suspect online drug sellers (Ivanitskaya et al., 2010). The investigators reasoned that if even American college students, who are savvy users of technology, and undergraduate students of health science, who are well educated about health, could be deceived by internet pharmacies, then how much greater the risk to the average consumer (Ivanitskaya et al., 2010)? They found that participants were quickly deceived by professional-looking websites and unsuspicious of very low list prices. Sixty percent of respondents attributed the low prices to fewer regulatory restrictions; 16 percent thought people should be advised to buy drugs on the internet to save money (Ivanitskaya et al., 2010).

This committee commends the NABP on the VIPPS accreditation system for online pharmacies. This system should be more widely promoted as a valuable consumer tool. Beyond promoting the verified pharmacies, it is unclear what novel actions could better control internet drug sales. One possible solution is asking Congress to make all online pharmacies illegal except for the VIPPS-accredited ones (Shelton, 2012). There is no value,



The Verified Internet Pharmacy Practice Sites logo.
SOURCE: NABP, 2012.

however, to an unenforceable law, as legislation about internet pharmacies would be.

To complicate the problem, even unlicensed internet pharmacies have advocates who believe the stores empower them to avoid artificially inflated medicine prices (Wasik, 2012). They may maintain that individual importation from foreign pharmacies improves the competiveness of the drug market (Shepherd, 2007b). Taking advantage of these countries' price controls could, they reason, drive down prices in the United States (Shepherd, 2007b). However, internet importation is, at best, an exploitation of other countries' price controls (Shepherd, 2007a). At worst, it exposes patients to an unregulated medicine supply. Encouraging internet importation is also a shortsighted solution to American problems with drug pricing. As the director of the University of Texas Center for Pharmacoeconomic Studies explained, "Our high drug prices are our problem . . . not the problem of Canada or any other country" (Shepherd, 2007a, p. 1290).

Trustworthy, accredited online drug stores do not sell medicine more cheaply than any other registered pharmacy would. Steep online discounts attract customers but come from illegitimate vendors. In the United States, reducing the draw of unlicensed drug stores requires either regulating the internet, a fool's errand, or completely renegotiating national drug price controls, which is outside the scope of this report (deKieffer, 2006).

Controlling the sale of medicine is a complicated problem the world over. Some unlicensed vendors work in street bazaars; others sell on the internet. In either case, regulatory accreditation can help consumers by identifying the good-faith sellers. The NABP's VIPPS accreditation does this for trustworthy online drugstores in the United States; the EMA is working on a similar program for Europe. In developing countries, the most useful drug-seller accreditation programs are those that work with the private sector to improve retail, especially in rural areas and slums. Training and task shifting could also improve the quality of patient counseling and drug dispensing in low- and middle-income countries.

Consumer confidence in drug safety could be improved by strengthening the ability of every intermediary on the supply chain to track drugs' movement from the manufacturer to the patient. Understanding a drug's history and path is important, especially as it moves through the unpredictable wholesale market. The United States needs stricter drug wholesale and tracking requirements. Implementing changes to the American system would build momentum for stronger medicines regulation around the world.

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6

Detection Technology

This chapter provides an overview of the technologies commonly used to detect substandard and falsified drugs, ranging from inexpensive field assays to highly sophisticated laboratory methods. It does not describe every technique used or the pharmaceutical application of each technology, but rather explains how technology can be used to identify illegitimate drugs.

Modern science has opened up immensely powerful and expensive forensic chemistry techniques that can give investigators information on the unique fingerprints manufacturers leave on their products. Such an analysis can give prosecutors the evidence necessary to tie falsified drugs to particular sources, but such sensitivity comes at a cost. Forensic chemistry assays cost $5,000 to $15,000 per test on average (personal communication, Ben Paulson, Chemir, January 25, 2013). They are not practical for routine product quality market surveillance in any country and may be out of reach entirely in many of the low- and middle-income countries most affected by the problem (Fernandez et al., 2008; Power, 2008). Keeping in mind the high costs of these laboratory analyses, this chapter discusses inexpensive and sustainable detection technologies that can be used for routine product quality assessments in all markets.

QUALITATIVE AND QUANTITATIVE METHODS

Detection technologies provide varying degrees of qualitative and quantitative data about medicines. Qualitative techniques provide information about a drug's identity, such as its active ingredient, color, or labeling. Quantitative techniques provide information about a drug's content and

Key Findings and Conclusions

- As criminals become more sophisticated, there will be an increased need for expensive technologies to detect falsified medicines.
- There are several categories of techniques to analyze pharmaceuticals. They include visual inspection of product and packaging; tests for physical properties such as disintegration, reflectance spectroscopy, and refractive index; chemical tests including colorimetry and dissolution; chromatography; spectroscopic techniques; and mass spectrometry.
- Novel technologies are constantly being developed to detect falsified and substandard medicines.

how that content will be absorbed in the body. Qualitative assays may be used to quickly detect the least sophisticated falsified drugs, such as those with the wrong or no active ingredient. Quantitative deficiencies, such as an unacceptably high level of impurities or an unacceptably low or high dosage of active ingredient, are more common among substandard drugs. Tests for drug quality use both qualitative data (e.g., the identity of ingredients, the presence and nature of any packaging and inserts, the presence or absence of impurities, and any data referring to the drug's appearance) and quantitative data (e.g., the amount of an ingredient present, tablet hardness, the rate and extent of disintegration and dissolution, and measured levels of impurities).

A full evaluation of drug quality requires a range of qualitative and quantitative testing to verify the identities and amounts of active ingredients, check for impurities, and ensure acceptable disintegration, dissolution, stability over time, and sterility (USP, 2007). Identifying falsified and substandard drugs does not always follow the same process as a rigorous quality evaluation. A few simple tests can identify a product with no active ingredient or one made under gross manufacturing negligence. More sophisticated fakes resist easy detection. Appearance, content, and therapeutic effect can all be considered in classifying falsified drugs. Box 6-1 outlines one method for making categories.

Criminals in the business of making falsified drugs can buy crude active ingredients, chemicals that have not undergone the appropriate purification steps required to meet pharmacopeial standards or manufacturer's dossier requirements, for example. The drugs made from such chemicals would pass most tests. Only highly sophisticated and expensive assays could de-

BOX 6-1
Classifying Falsified Medicines

One way to classify falsified medicines is to assign categories based on the sophistication of the fake. This is an example of such categorization.

- *Category 1:* Completely fraudulent products with unknown contents and therapeutic effects significantly different from the genuine drug.
- *Category 2:* Look somewhat similar to the drug being imitated, but the drug composition is not known.
- *Category 3:* Look very similar or identical to the genuine product but contain an entirely different drug, if any.
- *Category 4:* Look very similar or identical to the actual product but contain an alternative drug or synthetic analogue providing similar therapeutic value to that of the authentic product; intended to create repeat business.
- *Category 5:* Visually identical, highly sophisticated copies or synthetic analogues with some therapeutic value that cannot be detected using most field and laboratory methods.

tect trace contaminates. Figure 6-1 gives an overview of the different levels of technology needed to catch progressively more complex falsified drugs.

Overview of Detection, Screening, and Analytical Techniques

The main categories of techniques for pharmaceutical analysis can be broken down as follows: visual inspection of product and packaging; tests for physical properties such as disintegration, reflectance spectroscopy, and refractive index; chemical tests including colorimetry and dissolution; chromatography; spectroscopic techniques; and mass spectrometry. Within each of these categories, some technologies are appropriate for use in the field with minimal training, while others require sophisticated lab equipment and a high level of technical expertise.

Visual Inspection and Package Technologies

An expert can identify some drug quality problems by sight. Therefore, visual inspection of a product and its packaging by someone who knows the properties of the authentic drug or is able to compare the sample to

FIGURE 6–1 More sophisticated fakes require more sophisticated technologies to detect them.
NOTE: HPLC = high-performance liquid chromatography; TLC = thin layer chromatography; UV = ultraviolet.

the authentic product is the standard first step in any drug quality analysis (Martino et al., 2010). These visual inspections provide qualitative data about drugs' identities. Differences from the authentic materials in color, size, shape, tablet quality, and packaging indicate a possible falsified or substandard drug. These differences range from subtle to obvious. An educated consumer could probably identify a very-poor-quality fake, such as a pill of entirely the wrong color or shape, if they knew some properties of the authentic product, but even experts struggle to recognize more subtle inconsistencies. The Global Pharma Health Fund's Minilab toolkit promotes visual inspection as the first step to identifying falsified and substandard drugs but admits that this is challenging even for experts (Jähnke et al., 2008; Sherma, 2007). In recent years, criminals have produced very accurate reproductions of legitimate packaging. And, as Chapter 4 mentions, poor-quality drugs can sometimes be hidden in legitimate packaging (Sherma, 2007).

Visual inspection of a product can yield useful information, however. Some substandard drugs are of visibly low quality. Tablets that are cracked or falling apart are products of poor manufacturing practices (Kaur et al., 2010). Falsified drugs' packaging may have missing or misplaced expiry dates, lack instructions or manufacturing information, not have a batch number, or differ from the genuine packaging in many other ways. Sometimes poorly written instructions and spelling errors expose fake medicines; poor-quality inks may dissolve in water (Kaur et al., 2010). Similarly, the drugs may be the wrong color, size, or shape, have the wrong markings on them, have a different coating or texture, or be otherwise different from what is expected (Kaur et al., 2010). Sometimes the differences are obvious: fake Viagra seized in Hungary was pink instead of the well-known blue color of the genuine product. Further analysis revealed that the tablets contained 15 milligrams of amphetamine instead of the correct active ingredient (U.S. Drug Enforcement Administration Office of Forensic Sciences, 2004).

Visual inspections are often unreliable because substandard and falsified drugs and their packaging often appear identical or very similar to the genuine products. Criminals have copied holograms, barcodes, packaging styles, and tablet colors and markings with astonishing accuracy (Lim, 2012). Microscopic packaging analysis can identify some of these very careful copies. Under magnification, fine differences in printing, imprints, and alignment become clear. Figure 6-2 shows a high-magnification comparison of the lettering on a legitimate and fake blister pack. As this illustration suggests, visual inspection alone is not adequate to test for drug quality (Lim, 2012; Martino et al., 2010). Though a trained inspector can draw conclusions about drug quality by visual inspection, physical analysis is generally a more reliable way to identify fakes.

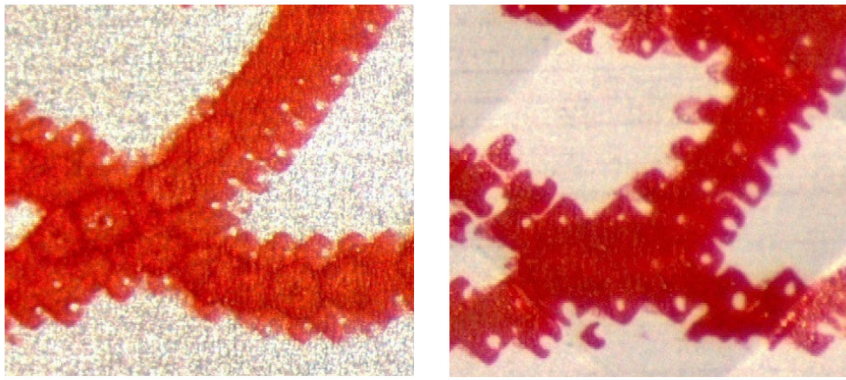


FIGURE 6-2 The printing on a fake Cialis blister pack is less crisp at 32× magnification.
SOURCE: Lim, 2012.

Physical and Bulk Property Testing

As Chapter 4 explains, active ingredients are the most expensive component of drugs; dilute or impure active ingredients can translate into vastly increased profits for an unscrupulous manufacturer. Some tests that rely on pH and other bulk properties can help identify active ingredients. Bulk properties, also called intensive properties, are properties that do not depend on the amount of the chemical sampled. Density, solubility, reflectance spectra, refractive indices, and optical rotation are examples of bulk properties (Brown et al., 2011). The malaria drug artesunate, for example, has some distinctive physical properties: It yields characteristic crystals when precipitated from water, and its extract acidifies water (Deisingh, 2005; Newton et al., 2006). These properties can be used to distinguish some authentic and fake antimalarials.

The refractive index, the measure of how light passes through a substance relative to the speed at which light passes through a vacuum, is a similarly useful bulk property. The refractive index can be used to measure the purity of pure liquids and can detect materials separated by liquid chromatography. Field inspectors can use handheld refractometers to measure the refractive index and use it as a quantitative test for some active ingredients (Kaur et al., 2010). Green and colleagues explored the practical use of refractive index to measure the amount of active ingredients selectively dissolved in certain solvents (Green et al., 2007). They found that while the refractive index can measure the amount of an unknown active ingredient, colorimetry can be used to help confirm its presence (Green et al., 2007).

Colorimetry and Other Chemical Testing

A variety of simple chemical reactions can test for the presence of active ingredients. Colorimetry is one such technique. It relies on chemicals that undergo color changes when reacted with certain compounds to provide qualitative data about a drug's identity. Colorimetry protocols exist for the active ingredients in many essential drugs. Fast Red TR dye tests for the active ingredient in some antimalarials by turning yellow in the presence of artesunate (Green et al., 2001). In addition to verifying the presence of an active ingredient, colorimetry can serve as a semi-quantitative technique to provide information about tablet potency; a more drastic color change or deeper color generally indicates a larger amount of ingredient. More precise colorimetric testing is possible with a handheld photometer, a spectroscopic device that measures absorbance of light through a substance (Newton et al., 2006). Colorimetry gives limited information and destroys the sample under investigation, but it is invaluable to field inspectors because it is an inexpensive technique that requires very little training.

Disintegration and dissolution testing may identify common formulation problems. Disintegration tests measure how rapidly solid dosage forms disintegrate in a solution; dissolution tests analyze the rates at which drugs dissolve (USP, 2007). Dissolution tests require more training than colorimetry and disintegration testing but may help predict the bioavailability of drugs, an important aspect of their efficacy. If a drug has poor dissolution, then the target dose of active ingredient may not be available to the patient. Incorrect excipient formulation, poor-quality manufacturing, and improper storage conditions can all lead to poor dissolution (Kaur et al., 2010). Even if the drug contains the correct dose of active ingredient, disintegration and dissolution tests may be able to identify an illegitimate drug (Deisingh, 2005). Disintegration tests are fairly simple and can be done in the field, but dissolution tests require sophisticated equipment (Kaur et al., 2010).

Chromatography

Chromatography separates mixtures into their constituent parts based on a variety of chemical and physical properties. It can be used to separate drug ingredients for further testing and, when used with appropriate detectors, provides both qualitative and quantitative information about active ingredients and impurities (Kaale et al., 2011). Chromatography is therefore the most common analytical method used in drug evaluations (Martino et al., 2010). Chromatographic techniques range from basic techniques, such as thin layer chromatography (TLC) with visual inspection, to more specialized laboratory methods, such as high-performance liquid chroma-

tography (HPLC) coupled with mass spectrometry. Like colorimetric tests, chromatographic analysis destroys the drug sample.

TLC is a planar chromatographic technique that is ideal for field drug testing (Martino et al., 2010). In TLC comparisons, authentic samples travel the same distance on a TLC plate and yield main spots of highly similar shapes, colors, intensities, and sizes as reference standards. TLC is a qualitative and, when used with visual detection, semi-quantitative technique. The distance the sample travels is associated with its identity; the intensity of the spot correlates with the amount of the drug present. High concentrations of impurities may be visible on a TLC plate as well (Kaur et al., 2010). In a convenience sample of tuberculosis drugs in Botswana, TLC indicated 31 percent of the samples tested were substandard (Kenyon et al., 1999). In China, researchers used TLC to distinguish between authentic and falsified versions of several antibiotics (Hu et al., 2005).

TLC is an uncomplicated assay useful in developing countries because it yields "versatile and robust" results at a low cost (Kaale et al., 2011). Each TLC plate costs about $2, and most solvents used in TLC are common and inexpensive. The plates are only used once, preventing contamination and limiting maintenance requirements (Kaale et al., 2011). Compared to other chromatographic techniques such as HPLC, TLC requires significantly less equipment and expertise. Modern instrumental TLC applications give quantitative assessments similar to those obtained with other instrumental chromatography procedures. High-performance TLC is a more effective and efficient version of TLC. Disposable HPLC plates cost about $15 each but can run 18-36 samples at the same time (Kaale et al., 2011).

The main drawbacks to TLC are its limited semi-quantitative data (when used with visual detection) and the need for accurate technique (Kaale et al., 2011). TLC solvents are often toxic or flammable, so these chemicals may be difficult to transport for field use. Furthermore, TLC provides limited information about a drug's identity; two samples that travel different distances are definitely not the same substance, but two different substances could appear identical using any chromatography technique if they are chemically similar enough. The inspector running the TLC assay must spot the plate correctly with the sample, which requires some training, and then compare the results to those obtained with reference standards. Accurately estimating the amount of drug on a TLC plate can be difficult without experience (Kaale et al., 2011). Despite its limitations, a trained operator can glean significant information from a TLC experiment with visual detection (Jähnke et al., 2001; Kaale et al., 2011).

Advanced chromatography techniques HPLC is a more selective technique and, when coupled with sensitive detectors, is generally regarded as the definitive technique for drug content analysis (Martino et al., 2010).

Depending on the associated detection technology, it can be expensive and require skilled operators and expensive, often scarce, solvents. The systems also require reliable electrical power, which can be an obstacle in developing countries.

Figure 6-3a shows an HPLC chromatogram that clearly distinguishes between the antimalarials chloroquine, mefloquine, and quinine. Although the drugs are chemically similar (see Figure 6-3b), mefloquine is significantly more expensive, and the cheaper drugs are sometimes sold labeled as mefloquine (Gaudiano et al., 2006). HPLC can identify and measure active ingredients and many impurities, but may not detect excipients that are not soluble in the mobile phase. It can be used with an array of detection technologies such as mass spectrometry and UV-visible spectroscopy (Martino et al., 2010).

Diode array detection is now standard with many HPLC assays and can be used to confirm the presence of active ingredients. It is a type of UV spectroscopy that is particularly useful because it can operate at varying wavelengths, allowing it to be fine-tuned for analyses, and can help detect the presence of several components hidden in a single HPLC peak (Kazakevich and McNair, 1996). Titier and colleagues developed an HPLC with diode array detection method to detect and quantify eight antidepressants for use in cases of suspected poisonings (Titier et al., 2003). The main advantages of the method were its speed, ease of use, and accuracy.

Gas chromatography, the most powerful chromatographic technology, provides similar information as the other chromatography systems. However, it may only be used for separation of volatile materials, such as residual solvents, undeclared ingredients, and any volatile impurities. This technique can only be used when the compounds of interest are gaseous in the analytical temperature range and do not degrade at or before the assay's minimum temperature. For example, artemisinin derivatives for treating malaria are too unstable for gas chromatography (Martino et al., 2010).

Investigators can use gas chromatography to develop profiles of drugs' volatile impurities and use those profiles to link batches of drugs from the same source. The great deal of natural variation in impurities allows this; even batches of genuine product from different sources are distinguishable, and the same is true among different falsified and substandard versions. In a review of the forensic applications of impurity profiles, Mulligan and colleagues concluded that drugs with very similar impurity profiles may be from the same place. Statistical analysis of impurity data can determine the probability that different samples have a common source (Mulligan et al., 1996).

Unlike TLC, advanced chromatography techniques require considerable investment; the equipment needed is expensive to buy and maintain (Kaale et al., 2011). These tests can only be done in central laboratories,

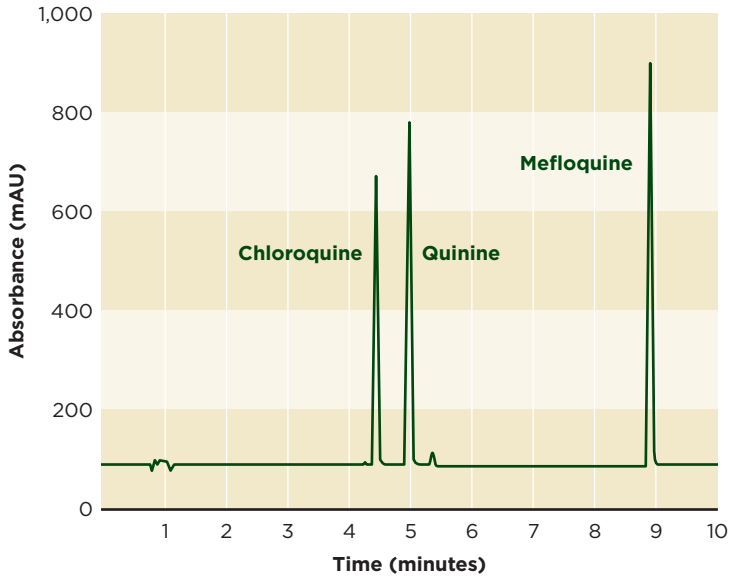
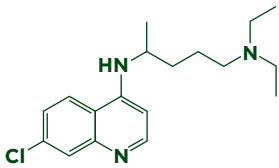


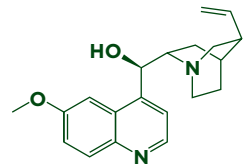
FIGURE 6–3a An HPLC chromatogram with distinct peaks for chloroquine, quinine, and mefloquine can be used to identify cheap chloroquine and quinine treatments labeled as the more expensive mefloquine.

NOTE: HPLC = high-performance liquid chromatography; mAU = milli absorbance unit.

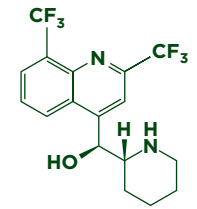
SOURCE: Adapted from Gaudiano et al., 2006. Reprinted with permission from Elsevier.



Chloroquine molecule



Quinine molecule



Mefloquine molecule

FIGURE 6–3b The similar chemical structures of chloroquine, quinine, and mefloquine.

and countries most affected by falsified and substandard drugs have limited access to such facilities (IOM, 2012). HPLC and gas chromatography are time-consuming, especially considering the time spent preparing the samples for analysis. The return on the time investment is mixed, as chromatography separates a minimum number of components present in a sample. A peak assumed to represent one compound may be hiding several other compounds.

Spectroscopy

Spectroscopy is a class of analytical techniques that measures the interaction of matter and radiation, thereby giving insight into chemical structure and contents. These techniques all provide qualitative data, and some provide significant quantitative data as well. Often referred to as the chemical fingerprints of drugs, the various spectra produced using these techniques elucidate different aspects of drug composition; characteristic absorption or emission peaks correspond to aspects of chemical composition and molecular structure. A chemist can extract detailed chemical and structural information from a spectrum, and an inspector with minimal training can also identify falsified and substandard medicines by comparing the drug spectra to reference materials in drug spectra databases (Kaur et al., 2010). The WHO maintains a digital version of the International Pharmacopoeia with drug quality determination protocols for many common medicines (WHO, 2011). This guide includes a reference infrared spectrum for each drug.

Molecular vibration and rotation energies occur in the infrared regions of the electromagnetic spectrum, and these movements may be observed with infrared, near-infrared, or Raman spectrometers. These techniques are relatively straightforward to use and moderately expensive, and routine comparative applications do not require extensive training. Chemists analyze the absorption peaks in these spectra primarily to identify molecular functional groups; most active pharmaceutical ingredients and some organic excipients and impurities have characteristic spectral peaks or spectral fingerprints that can be used to help identify them.

Infrared spectroscopy The infrared range of the electromagnetic spectrum can be divided into three subregions: the near-infrared, mid-infrared, and far-infrared. The mid-infrared range is the more discerning and commonly used region (Deisingh, 2005). Figure 6-4 shows the different infrared spectra of the antimalarial artemisinin and its derivative, artemether. This comparison can identify the common substitution of artemisinin for more effective and expensive antimalarials (Kaur et al., 2010).

There are several ways to collect infrared spectra, each having ad-

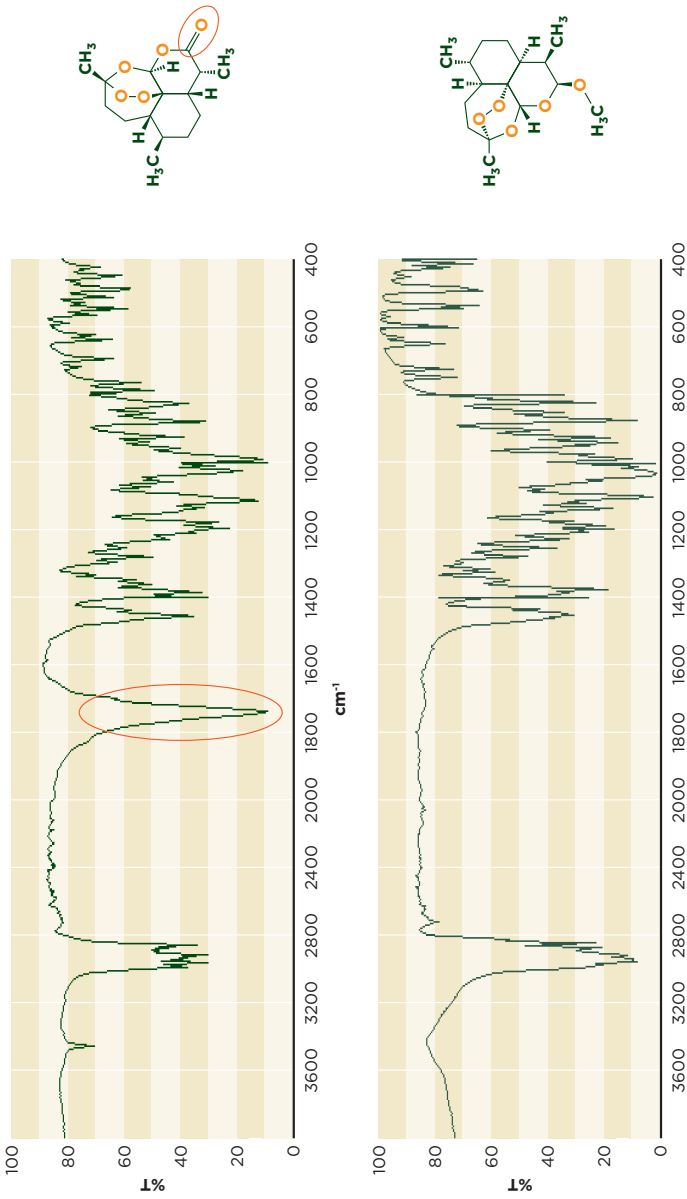


FIGURE 6–4 Infrared Spectra for artemisinin (top) and artemether, an artemisinin derivative (bottom) illustrate differences in their chemical composition. Artemisinin's carbonyl (C=O) functional group, missing from the derivative molecule, produces a characteristic peak between 1700 and 1800 cm^{-1}.

NOTE: cm^{-1} = wave number; %T = percent transmittance.

SOURCE: Spectra from WHO, 2008.

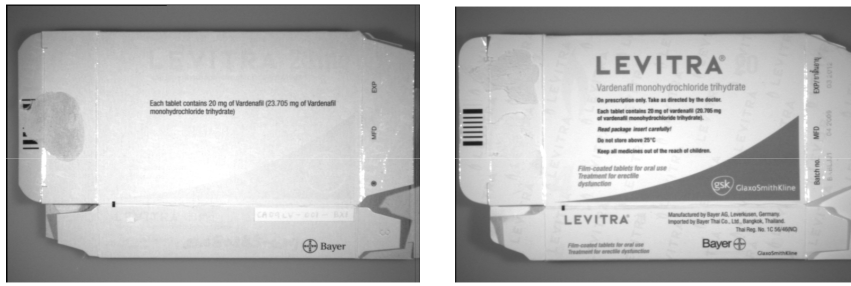


FIGURE 6-5 Use of FT-IR spectroscopy to distinguish between real (left) and falsified (right) packaging in Singapore.
SOURCE: Lim, 2012.

vantages and disadvantages. Attenuated total reflectance and Fourier-transformation infrared (FT-IR) is particularly useful for drug quality analyses because it does not require sample preparation, does not destroy the sample, and provides information about the distribution of active ingredients and excipients on the surface of tablets (Martino et al., 2010). A creative application of FT-IR can distinguish between some types of real and falsified packaging. Some manufacturers label their packaging to take advantage of the fact that only inks that absorb in the infrared range will be visible under infrared radiation. In an example from Singapore (see Figure 6-5), an inspector could see only a small amount of writing on a genuine Levitra package under IR radiation but could see all of the text on a falsified package (Lim, 2012).

Near-infrared and Raman spectroscopy Recent developments of portable near-infrared and Raman spectrometers have led to an increase in the use of these techniques for drug quality analysis (Fernandez et al., 2011). Both techniques are nondestructive, fast, and require no sample preparation; radiation can pass through samples in blister packs (Kaur et al., 2010; Martino et al., 2010).

Near-infrared is better suited than mid-infrared to quantitative analysis of drug contents. Computer modeling can produce limited quantitative characterization from all vibrational spectroscopy, but near-infrared and UV-visible spectroscopy yield more reliable quantitative data (Hsu, 1997). Near-infrared can identify active ingredients and is particularly useful for detecting incorrect concentrations of excipients, a common inconsistency in falsified and substandard drugs (Deisingh, 2005). When used with imaging techniques, near-infrared can yield information about a tablet's composition. Koehler and colleagues demonstrated this by comparing images of a pain relief tablet, one captured using near-infrared imaging and the other

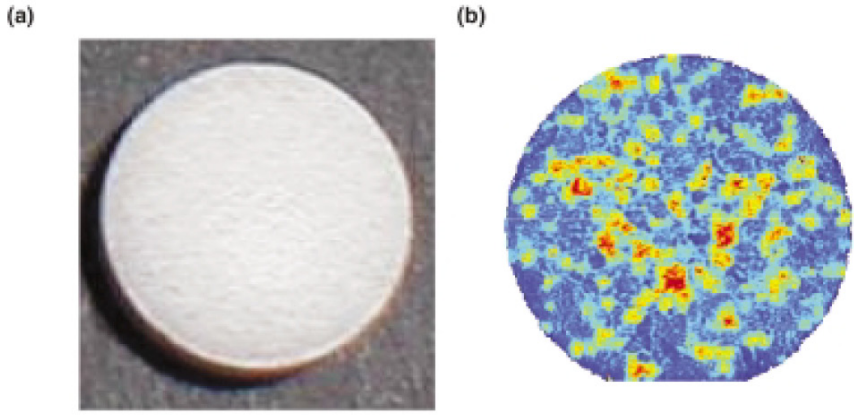


FIGURE 6-6 Image (a) is a pain relief tablet, image (b) its near-infrared spectra. The red spots indicate active ingredient and other colors indicate other ingredients.
SOURCE: Adapted from Koehler et al., 2002. Reprinted with permission from John Wiley & Sons, Ltd.

not, and illustrating that the homogenous-looking tablet surface actually contained a heterogeneous mix of active and inactive ingredients (see Figure 6-6) (Koehler et al., 2002).

Near-infrared spectra of two different compounds are often only subtly different, and accurately interpreting results may require significant training (Martino et al., 2010). Portable, battery-powered near-infrared spectrometers are a more accessible alternative to traditional spectrometers (Dowell et al., 2008). Bate and colleagues compared the effectiveness of a handheld model to TLC and disintegration tests and found that the handheld spectrometer detected significantly more poor-quality antimalarial drugs and antibiotics than the other tests (Bate et al., 2009a). The model they used weighed 4 pounds and contained a battery that could operate for 10 hours after a full charge, making it a powerful field tool (Bate et al., 2009a).

Raman spectroscopy can readily identify many active ingredients and give further information about excipients, as well as the relative concentration of active ingredients to excipients (Deisingh, 2005). These ratios can be key to detecting falsified and substandard drugs, because criminal manufacturers often take care to use the correct amount of active ingredient but may not be as exacting about the excipients, which may vary even among genuine manufacturers (Deisingh, 2005; Nyadong et al., 2009). For example, artesunate tablets may contain either of the highly similar sugars lactose or sucrose, depending on the manufacturer (Nyadong et al., 2009). Raman can distinguish between these, and a Raman spectrum of Cialis identifies both the active ingredient, tadalafil, and the primary excipient, lactose (Lim, 2012). Raman spectroscopy is particularly useful for detecting

inorganic substances in drugs, such as titanium dioxide, a common component of tablet coatings (Witkowski, 2005).

On the other hand, some blister packs, capsule materials, and tablet coatings can interfere with Raman scattering and make readings difficult (Martino et al., 2010). If the materials used produce fluorescence, they interfere with Raman signals, especially those read with handheld Raman spectrometers. Though far more widely available and useful for field inspections, these portable devices have less tolerance for fluorescence than their full-sized counterparts. This is especially problematic in screening antimalarials, as artesunate is somewhat fluorescent (Martino et al., 2010). But some investigators maintain that the fluorescence of genuine artesunate can serve as a tool to distinguish between good- and poor-quality samples, as those without sufficient active ingredient will not produce as much fluorescence (Ricci et al., 2008). Ricci and colleagues found that fluorescence interfered more with their readings on the handheld scanner, but it ultimately produced as reliable results as the Fourier-transformed Raman scanner (Ricci et al., 2008).

Nuclear magnetic resonance Nuclear magnetic resonance (NMR) spectroscopy analyzes the interaction of nuclei with electromagnetic radiation

A handheld Raman spectrometer.
SOURCE: Zook, 2012.

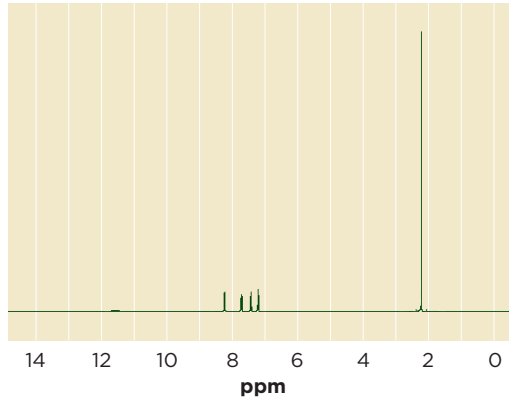


FIGURE 6–7 Proton NMR spectrum of aspirin (o-acetoxybenzoic acid).

NOTE: NMR = nuclear magnetic resonance; ppm = parts per million.

SOURCE: SBDSWeb.

while in magnetic fields. Like Raman and near-infrared spectrometry, it is a nondestructive, reliable technique, applicable to nuclei that have a nonzero spin, such as those in hydrogen and carbon-13, that yields quantitative data with little sample preparation. Figure 6-7 shows an NMR spectrum for o-acetoxybenzoic acid, the active ingredient in aspirin.

However, NMR instruments are expensive and require stable electrical power supplies, controlled temperatures, and skilled analysts for their operation. Integrating the area under each absorption peak can provide detailed information about molecular composition and structure; the area under each peak corresponds to the number of nuclei (in protons or carbon-13 atoms) contributing to that particular signal. Many common chemical contaminants produce characteristic absorption peaks (Gottlieb et al., 1997).

In NMR analysis, all of the compounds in the mixture (including active ingredients, excipients, and impurities) that contain the nucleus under analysis will contribute to the spectrum. This can produce ambiguous spectra that may contain overlapping signals, so chemists typically isolate the components before analyzing them with NMR. However, newer, more sophisticated NMR technologies may be capable of separating drug components and producing clearer signals. Diffusion-ordered proton-NMR spectroscopy, for example, can identify the various types of ingredients in a mixture by taking advantage of differences in molecular mass (Martino et al., 2010). The downside to this type of technique is that it is not quantitative, like normal NMR is, but, by using the two techniques together, a

fuller, clearer molecular picture can be developed. Using these methods, scientists have successfully differentiated between many authentic and falsified versions of antimalarials, erectile dysfunction drugs, and antidepressants (Martino et al., 2010).

X-ray diffraction and X-ray fluorescence are other techniques that can give substantial information about drug contents. X-ray diffraction can be used to analyze active ingredients and excipients, while X-ray fluorescence is used for elemental analyses that can often distinguish real from falsified drugs (Kaur et al., 2010; Martino et al., 2010).

Mass Spectrometry

Mass spectrometry, generally called mass spec, is a sophisticated analytical technique that requires extensive training and expertise to use. It provides abundant structural information and the precise molecular weight of the compound under investigation. Mass spec can identify many active ingredients and excipients, as well as some impurities (Kaur et al., 2010; Martino et al., 2010). This technique successfully detected falsified halofantrine syrup, an antimalarial, in West Africa that instead contained a sulphonamide antibiotic (Wolff et al., 2003). When mass spectrometers were the size of a dishwasher (Stroh, 2007), their value in the poorest countries was hard to realize, but newer, portable machines can take this sophisticated technology into the field (Yang et al., 2008). However, mass spectrometers require a stable electrical power source, which may be difficult to obtain in some developing countries.

An isotope ratio mass spectrometer provides detailed information about the abundance of various elemental isotopes. Many elements have naturally occurring isotopes that are present in minute quantities in any sample. The exact ratio of isotopes varies over time and space and with different production techniques. Isotopic ratios have been able to distinguish different sources of drugs and therefore may be useful for combating highly sophisticated copies (Lim, 2012). Regulators and law enforcement can use isotopic ratios to connect seemingly disparate events and build evidence that separate drug seizures have a common source. Documenting the isotopic ratios of a selection of common elements, such as carbon, hydrogen, oxygen, or nitrogen, can help identify these patterns (Lim, 2012).

Other kinds of mass spectrometry (e.g., direct ionization, tandem, time-of-flight, secondary ion, and electrospray ionization [ESI]) can be used alone and in combination with other analyses to detect illegitimate drugs (Deisingh, 2005; Martino et al., 2010; Wolff et al., 2003). Direct ionization mass spec, for one, is a relatively new class of mass spectrometric analysis that does not require lengthy sample preparation. Other techniques, such as direct analysis in real time (DART) mass spec and desorption ESI mass spec,

can identify correct and incorrect active ingredients and some excipients. Desorption ESI mass spec in particular provides information about tablet surface homogeneity and the distribution of active ingredients and excipients in or on the surface of a tablet (Martino et al., 2010). For example, an artesunate sample with homogeneous surface distribution of lactose and paracetamol, a fever reducer, is illegitimate; an authentic, good-quality sample should have homogeneous distribution of artesunate and scattered distribution of lactose (Martino et al., 2010).

The most sophisticated drug copies may resist identification with any technology other than mass spectrometry. Among these are very close analogues of genuine active ingredients. These analogues can be so chemically and structurally similar that they behave the same under nearly any analysis. Mass spectrometry's ability to precisely measure molecular weight and compare fragmentation patterns can help distinguish between compounds that differ by only one or two atoms. For example, the erectile dysfunction drug Cialis is often copied with varying degrees of sophistication (Putze et al., 2012; Trefi et al., 2008). U.S. Food and Drug Administration (FDA) forensic chemists have discovered several analogues of the active ingredient, tadalafil, in so-called herbal remedies (Gamble et al., 2008). Figure 6-8 compares the molecular structure of one such analogue, aminotadalafil, to tadalafil. The two differ only by the substitution of an amino (-NH_2) group for a methyl (-CH_3) group, making aminotadalafil slightly heavier. The health threats posed by such products have led researchers to investigate ways of reliably detecting and identifying these illicit drug compounds; other sophisticated techniques have been shown to detect some analogues, but the high specificity and sensitivity of mass spec makes it the most popular method (Singh et al., 2009; Venhuis and Kaste, 2012).

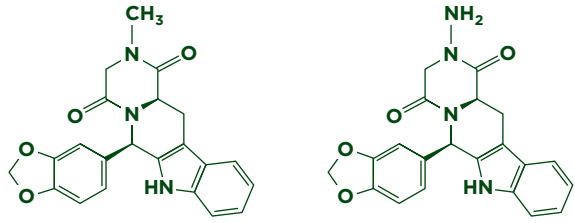


FIGURE 6–8 Nearly identical analogues of tadalafil (left, 389.40 g/mol), aminotadalafil (right, 390.39 g/mol). The only difference between the two compounds is the substitution of an amino group for a methyl group.

Emerging Technologies

Innovative technologies to detect falsified and substandard drugs are constantly emerging. Many of the most promising examples draw from a range of scientific disciplines. Researchers in Pakistan found that the relative susceptibility of ofloxacin-sensitive bacteria to various samples of ofloxacin is a good indicator of drug quality (Iqbal et al., 2004). A team of researchers from U.S. Pharmacopeia and Boston University is developing another new technology called PharmaCheck (see Box 6-2). PharmaCheck uses microfluidics, the control of fluids at a sub-millimeter scale, for rapid field drug testing (EurekAlert, 2012). PharmaCheck, which will weigh less than 10 pounds and fit in a shoebox, promises to greatly reduce the need for confirmatory laboratory testing (Barlow, 2012; Gaffney, 2012).

Capillary electrophoresis, a separation technique, has recently been

BOX 6-2
PharmaCheck

In a combined effort with the U.S. Pharmacopeial Convention, the United States Agency for International Development (USAID), and the Wallace H. Coulter Foundation, Muhammad Zaman of Boston University has been developing a PharmaCheck, a portable drug analysis device (Barlow, 2012). Called a "pharmaceutical lie detector" by the campus newspaper *BU Today*, Zaman's machine uses fluorescence and imaging technologies to measure a sample's potency (Barlow, 2012). The current prototype is the size of a shoebox, uses solar energy or battery power, and is designed as an "easy-to-use, robust system" for drug companies, nongovernmental organizations, and government agencies, among others (Barlow, 2012; Seiffert, 2012). Although originally developed for testing often copied malaria drugs, PharmaCheck will also be able to test other kinds of medications (Barlow, 2012). Zaman has said that the device should be undergoing testing in developing countries by early 2013 (Seiffert, 2012).

Saving Lives at Birth, a project developed by USAID, the Norwegian Ministry of Foreign Affairs, the Bill & Melinda Gates Foundation, Grand Challenges Canada, and the UK Department for International Development, runs a competition designed to find and support innovations in care for mothers and newborn children in developing countries (Saving Lives at Birth, 2012a,b). The organization recognized PharmaCheck's potential with a $250,000 grant given to Zaman and his partners over the next 2 years to further develop the device, one of only 15 projects chosen out of the more than 500 applications (Saving Lives at Birth, 2012c; Seiffert, 2012).

demonstrated to be a useful tool in the process of analyzing suspect pharmaceuticals (Marini et al., 2010). Staub and colleagues developed a capillary electrophoresis system paired with time-of-flight mass spectrometry for analyzing protein-based drugs, such as insulin, without sample preparation (Staub et al., 2010).

Researchers at King's College London and Lund University in Sweden have received a Translation Award from the Wellcome Trust to help bring their portable nuclear quadrupole resonance (NQR) device to market (Wellcome Trust, 2012). Based on technology similar to nuclear magnetic resonance spectroscopy, NQR uses radiofrequencies to provide qualitative and quantitative information about medicines and can scan them through packaging (Wellcome Trust, 2012; Wilkinson, 2012). Unlike most other techniques, NQR can analyze large quantities of medicine (an entire bottle or package) at one time (Barras et al., 2012). Radio wave technologies similar to those used in bomb detection are also being tailored for pharmaceutical analysis (Sprey, 2010).

USING TECHNOLOGY

The previous section outlined the main categories of techniques for detecting falsified and substandard drugs. A summary of a selection of the techniques discussed is presented in Table 6-1. Understanding when, where, and why to use the various techniques can be difficult. The information a technique provides, as well as its reliability, cost, required expertise, speed, and portability make it more or less appropriate in any given situation.

In order to conclude that a drug is of good quality, an inspector must test a sample for all of the main deficiencies of substandard and falsified drugs: fake packaging, incorrect color, shape, or markings, absent or incorrect active ingredients, incorrect quantities of ingredients, impurities, and reduced dissolution or disintegration. Table 6-2 outlines which classes of analytical techniques can test for these problems and how well they can be used in the field. In general, field use describes a relatively straightforward assay or technique that depends on portable or sturdy equipment. Most field methods can be used by professionals such as regulators, pharmacists, or health workers, but some, like mobile verification, are accessible to a layperson.

The Counterfeit Drug Forensic Investigation Network (CODFIN) uses a systematic analytical process to detect and classify substandard and falsified drugs (Fernandez et al., 2011). Figure 6-9 shows how investigators in the network test samples in national drug quality surveys (Fernandez et al., 2011). The steps shown in green can be done in the field, but samples are generally sent to a central laboratory for the steps show in brown (Fernandez et al., 2011). Fernandez and colleagues have used this system

TABLE 6-2 Product Quality Attributes and Assessments

Problems	Detection Techniques						
	Visual Inspection	*Package Technologies*	*Chemical or Microbiological Tests*	*Spectroscopy and Mass Spectrometry*	*Physical Measurements or Examination*	*Chromatography*	*Reflectance*
Absent or incorrect active ingredient			✓	✓	✓	✓	✓
Wrong color	✓		✓	✓		✓	✓
Wrong shape or markings	✓			✓			
Fake packaging	✓	✓		✓	✓		✓
Incorrect quantities of ingredients			✓	✓		✓	
Impurities			✓	✓		✓	
Dissolution			✓			✓	
Disintegration			✓				
Uniformity of dosage units			✓		✓	✓	
Microbial contamination	✓		✓				

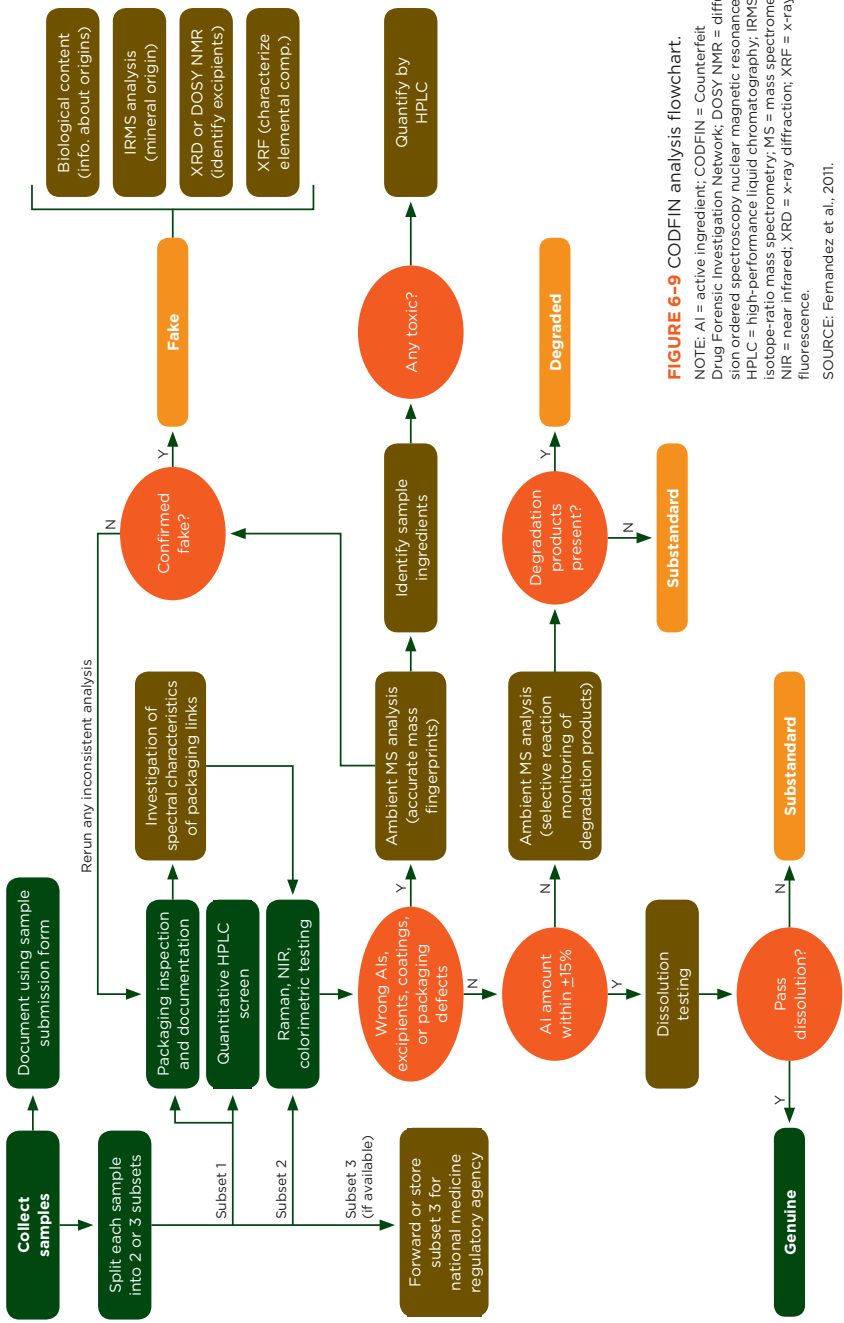


FIGURE 6–9 CODFIN analysis flowchart.
NOTE: AI = active ingredient; CODFIN = Counterfeit Drug Forensic Investigation Network; DOSY NMR = diffusion ordered spectroscopy nuclear magnetic resonance; HPLC = high-performance liquid chromatography; IRMS = isotope-ratio mass spectrometry; MS = mass spectrometry; NIR = near infrared; XRD = x-ray diffraction; XRF = x-ray fluorescence.
SOURCE: Fernandez et al., 2011.

Key Findings and Conclusions

- There is no single analytical technique that provides enough information to confirm that a drug is genuine, but combining techniques gives more precision.
- It is often difficult to test for drug quality in low- and middle-income countries. Poorly trained chemists and dilapidated infrastructure are common obstacles in performing accurate drug quality testing.
- Making detection technologies easily accessible in low- and middle-income countries will help curtail the trade in falsified and substandard medicines.
- Field technologies and techniques are useful for detecting most falsified and substandard drugs. They should be easy to use and maintain, cheap, and durable.
- The costs associated with developing new detection technologies are a barrier to having robust, sustainable, easy-to-use, and inexpensive technologies available in the field.

to investigate malarial drug quality in developing countries (Fernandez et al., 2011).

Combining Techniques

Although any one test may suffice to label a drug substandard or falsified, no single analytical technique provides enough information to confirm that a drug is genuine. Similarly, while colorimetry and TLC are field techniques for testing for the presence of a particular ingredient, knowing a sample's full content requires more testing. Spectroscopic techniques are useful for identifying active ingredients but cannot rule out the presence of countless possible impurities. Chromatographic techniques may suggest that the drug contains sufficient active ingredient, but they do not provide any information about how much of that active ingredient will reach the patient. Time and budget allowing, the best understanding of drug quality comes from the several complementary experiments.

Even combinations of techniques from within a class, such as spectroscopy, can be helpful. One study illustrated how, due to differences in the ranges of their spectral regions, infrared spectroscopy may at times be better at identifying organic substances in tablet coatings, whereas Raman spectroscopy may better identify the inorganic components (Witkowski, 2005). Experiments that looked at the coating on Cialis tablets found that

Klaus Boehm of Merck presents minilabs to Hiti Sillo, head of the Tanzanian Food and Drugs Authority.
SOURCE: GPHF, 2012e.

Raman spectroscopy did not distinguish between the real coating and falsified coating, but infrared spectroscopy did (Lim, 2012).

Chemists typically pair mass spec with separation techniques, such as HPLC, to achieve a more definitive analysis. These hyphenated techniques have broad capabilities. For example, liquid chromatography-mass spectrometry is a highly reliable separation technique, but does not directly provide quantitative data about the amount of active ingredient present; analysts must compare results to standards to determine content (Kaur et al., 2010). A type of combined gas chromatography and mass spec (GC-MS) can provide information missing in HPLC-MS analysis. Mulligan and colleagues found that automated equilibrium headspace sampling with capillary gas chromatography provides information about volatile impurities, but adding mass spec analysis provides extra qualitative information about the identity of any impurities present (Mulligan et al., 1996).

When Captagon, a stimulant drug popular in the Middle East, was outlawed, illegal manufacturers began selling the drug (Alabdalla, 2005). The copies were generally falsified drugs containing amphetamines and caffeine meant to mimic Captagon's therapeutic effects. Early investigations primarily relied on ultraviolet, infrared, and TLC analysis to determine the active ingredients in suspect tablets (Alabdalla, 2005). In 2005, Alabdalla and

colleagues used GC-MS analysis to further identify substitute ingredients, including chloroquine, ephedrine, caffeine, amphetamine, and methamphetamine (Alabdalla, 2005). The combined analysis also indicated, with reasonable certainty, which drugs were from the same batches (Alabdalla, 2005). Where applicable, GC-MS plots are an unequivocal way to identify substances (Rivier, 2003). Courts prefer them to other analytical techniques as forensic evidence (Rivier, 2003).

Combining analytical techniques is a challenge both in the field and in the laboratory. It is difficult to determine which tests can be combined to allow inspectors to use the minimum number of different techniques. It is usually best to work through tests beginning with the easiest or least expensive ones and to only move on to the more expensive or difficult tests if the sample passes the earlier ones. For example, a drug that fails an identity test does not need to be tested for the amount of incorrect active ingredient. This is the basis of the minimum testing scheme used by the Pharmaceutical Security Institute (USP, 2007).

Using Technology in Developing Countries

The question remains as to how to use analytical methods in parts of the world with limited laboratory capacity and trained chemists. Reliable reference materials to test samples against are often scarce in poor countries (Fernandez et al., 2011). Manufacturers are reluctant to release reference standards when they fear the information could be used to make an illegitimate drug. In any case, the most sophisticated analytic technologies were not designed for the field.

Field Technologies

Technologies for field detection of falsified and substandard drugs in developing countries must be portable, relatively simple to use, sturdy, and inexpensive to buy, use, and maintain. They must also provide reliable, useful data. Field techniques (including visual inspection, colorimetry, disintegration tests, TLC, and handheld spectrometry) can detect many falsified and substandard drugs. As the previous section explains, these techniques are durable, fast, relatively inexpensive, and fairly easy to use, making them attractive to regulators interested in monitoring drug quality. Box 6-3 describes the Chinese regulatory authority's mobile verification labs. Package verification technologies can also aid in field detection of falsified drugs, although these methods are useful more to the patient at the point of use than to the regulator.

The more reliable field analytic tools are also more expensive. Although fairly inexpensive TLC and disintegration testing are useful field techniques,

BOX 6-3
Chinese Mobile Laboratories

The Chinese drug regulatory authority uses mobile labs for drug surveillance (Jin, 2007). First used in Henan province in March 2006, mobile labs quickly spread to 29 provinces (Jin, 2007). The mobile lab program also trained 760 technicians to operate the labs, which bring drug screening technology to rural areas (Jin, 2007).

The mobile labs, housed in vans, can carry out rapid on-site screening of suspicious drugs (NICPBP, 2012). Each van carries chemical analysis technologies, including TLC systems, a near-infrared spectrometer, and portable computers (NICPBP, 2012). The vans also house information on 200,000 manufacturers, including names, addresses, and licensed products, as well as a provincial "Drug Quality Bulletin" with annually updated information on known poor-quality drugs (Jin, 2007). The labs' operations are designed to be simple, fast, and easily executed (NICPBP, 2012). A mobile lab can test the quality of more than 800 drugs, including antimalarials, antiretroviral, tuberculosis medication, other essential drugs, and traditional Chinese herbal medicines (Jin, 2007; NICPBP, 2012).

In the first 6 months of operation, mobile labs screened 110,426 batches of drugs and confirmed 3,122 of them to be substandard (Jin, 2007). The project's success has inspired the regulatory authority to help other countries develop similar mobile labs and to use them in drug procurement (Jin, 2007). Members of the Thai FDA, for example, visited Chinese mobile labs in 2006 (Jin, 2007).

A mobile lab in China.

according to Bate they are less reliable than handheld spectrometric devices (Bate et al., 2009a). Of 78 samples tested in one study, 17 passed both TLC and disintegration tests but did not pass either Raman or near-infrared spectroscopic analysis (Bate et al., 2009a). Field tests are no substitute for definitive laboratory techniques and cannot test all aspects of a product's quality, including its drug content, impurity profile, and dissolution profile.

Noting the cost of laboratory pharmaceutical testing and the dearth of qualified laboratories in developing countries, the German Pharma Health Fund (now known as the Global Pharma Health Fund) developed the Minilab, a portable quality-analysis laboratory described in Box 6-4 (Jähnke et al., 2001; Kaale et al., 2011). During a November 2012 Minilab training session in Angola, trainees tested an illegal shipment of various pharmaceuticals seized by customs officials along the African coast (Minilab Saves Lives, 2012; World Customs Organization, 2012). Using the TLC and visual inspection techniques, they identified many drugs with no or little active ingredient (Minilab Saves Lives, 2012). Merck S.A. in Portugal provided 10 Minilabs to Angola, which has no drug testing labs (Minilab Saves Lives, 2012). Other similar field kits also exist, such as the Thermo Scientific FirstDefender and TruDefender field laboratory devices used by the Singaporean regulatory authority (Lim, 2012).

Detection in Every Setting

There is a wide range of technology available to detect falsified and substandard drugs; a good prevention strategy makes use of a wide variety of them. As Chapter 5 describes, some technologies, such as scratch-off codes, can be used by the consumer. There are also package technologies manufacturers may use to distinguish their products at the point of purchase. Holograms and reactive ink are examples of such package technologies. Holograms can be convincingly copied, as illustrated in Figure 6-10, but may give customers an extra level of assurance. Similarly, Brazil requires all drug companies to mark packages with a scratch-off label made from a reactive ink (Filho et al., 2010), though participants at the São Paulo site visit for this study expressed consistent doubt that consumers were adequately informed about how to use the label.

Informed patients can assist in identifying falsified and substandard drugs. Visual inspection of drug packages and color can identify gross differences between authentic and fake medicines. Similarly, patients might detect microbial contamination, seen as black specks on the surface of the product with the naked eye, or notice defects in a drug's hardness when handling it. Table 6-2 describes the limits of visual inspection and other types of inspection.

Pharmacists are able to run a wider variety of tests to detect problems

BOX 6-4
The Global Pharma Health Fund Minilab

The Global Pharma Health Fund Minilab is a portable drug quality analysis toolkit (Kaale et al., 2011). The Minilab was designed to help control the proliferation of substandard and falsified drugs in countries with weak or absent regulatory systems (Jähnke et al., 2001).

The Minilab relies on a combination of accessible techniques for simple, fast, and reliable detection of falsified and substandard drugs. With the exception of running water and a flat surface on which to work, the kit contains all the labware, reagents, standards for comparison, and instructions necessary to run quality tests on many common medicines.

SOURCE: GPHF, 2012d.

with medicine quality. If properly equipped, a pharmacist can run colorimetric tests and TLC on suspect samples in the pharmacy. The pharmacist, or a lower-level pharmacy worker, is also key in monitoring the chain of custody in track-and-trace systems. Field inspectors can take a similar role, especially in places where there are few trained pharmacists. As Boxes 6-3 and 6-4 explain, mobile testing is an important piece of drug quality monitoring in much of the world. Field inspectors can use handheld spectrometers and Minilabs to evaluate drug quality.

Field inspectors feed useful information about drug quality into the regulatory system. Regulators have higher-level controls to detect poor manufacturing and product quality in the market. Ultimately, no detec-

Each Minilab fits into two suitcases for durable portability. Price and simplicity guided the kit's design; the solvents and reagents used in the assessments are safe for use with very little training and are widely available and inexpensive. Each Minilab quality test costs no more than $3 to run (GPHF, 2012c; Kaale et al., 2011).

The kit includes equipment and instructions for thin layer chromatography (TLC), chemical colorimetry, and disintegration tests, as well as a visual inspection protocol. Testing and inspection protocols and materials are included for more than 50 World Health Organization essential medicines, including reference standards for 63 drug compounds (GPHF, 2012a; Kaale et al., 2011). By using colorimetry, which tests for the identity of active ingredients, and TLC, which provides information about potency, the kit is capable of testing for the top three kinds of substandard and falsified drugs: those that contain no active ingredient, those that contain too little active ingredient, and those that contain the wrong active ingredient (GPHF, 2012c; Jähnke et al., 2001). Since the reliability of TLC is based in large part on the tester's level of training, the Minilab attempts to simplify the analysis by providing reference tablets that can be used to prepare 100 percent and 80 percent dosage strengths for comparison (Kaale et al., 2011).

Currently, there are more than 500 Minilabs in 80 countries, and many prominent national and international organizations recommend the kits for field testing (GPHF, 2012c). The U.S. Pharmacopeial Convention distributes and administers trainings for Minilabs in developing countries through its Drug Quality and Information program, in collaboration with USAID (Smine and Hajjou, 2009). The lab has also been used by the WHO's Roll Back Malaria program and by several local nongovernmental organizations in countries such as Tanzania and Ghana (Jähnke et al., 2001).

tion technology can replace stringent drug regulation in the fight against falsified and substandard drugs. The sentiment that no one can test quality into drugs is true to a certain extent. It is important to be able to test drug quality, but also important to impose good manufacturing practices on companies to prevent quality problems before they arise. However, effective use of technology can help improve drug quality. A study on drug quality in Nigerian pharmacies before and after handheld spectrometers were distributed indicated that drug quality improved when testing became more reliable and convenient (Bate and Mathur, 2011).

Making detection technology more accessible in low- and middle-income countries is invaluable to controlling the trade in falsified and sub-

FIGURE 6-10 Genuine (left) and falsified (right) holograms on artesunate blister packs found in Southeast Asia.
SOURCE: Newton et al., 2008.

standard drugs. Technologies can protect consumers and also help generate accurate estimates of the magnitude of the problem. An understanding of the technological landscape, the range and gaps in available technologies, and the likely improvements in the near future is necessary for using technologies in developing countries.

The Technological Landscape

Technology is a constantly evolving field. New techniques developed specifically for detection and analysis are always emerging. As some of the standard assessment techniques become smaller, lighter, cheaper, and more durable, the boundary between field and laboratory testing is blurring. Navigating the technological landscape is a formidable challenge, especially in low- and middle-income countries. The committee believes that interdisciplinary collaboration yields the best and most efficient advances in detection technologies, especially technologies that can be useful in developing countries.

Regulators in these countries have relatively infrequent opportunities to interact with academic and industry experts (IOM, 2012). Working in relative isolation translates into few opportunities to advocate for research on their behalf. This chapter gives some overview of the detection technologies that exist now, but a different expert working group could better articulate what technologies will be useful in the future. It is also unclear under what conditions the cost-to-benefit analysis favors the use of different detection technologies.

Recommendation 6-1: The National Institute of Standards and Technology should fund the development of a central repository for existing and newly innovative detection, sampling, and analytical technologies, ranging from field and rapid screening technology to sophisticated laboratory-based assessments, to identify substandard and falsified medicines.

The cost of development is the main barrier to having robust, sustainable, easy-to-use, and inexpensive detection technologies available in the field. The committee believes that public funding for development would direct academic interest and attention to this important problem. The National Institute of Standards and Technology (NIST), a division of the Department of Commerce, has the depth in physical and materials science necessary for developing and adapting drug testing technologies (NIST, 2008). The institute is committed to innovative interdisciplinary research for bioscience and health (NIST, 2010). Drug quality analysis draws from

At a Minilab training session in Angola, field inspectors learn how to test drug quality.
SOURCE: Minilab Saves Lives, 2012.

material, basic, and computer science, and a range of engineering disciplines. The FDA and the pharmaceutical industry also have technical depth in these areas, and they should work with NIST on a technical working group about drug detection technologies. The NIST has worked closely with the FDA before, such as in their work on the measurement of drug delivery systems with secondary ion mass spectrometry (NIST, 2009a).

Every year, the institute's Small Business Innovation Research (SBIR) program awards contracts to small businesses for science and engineering research (NIST, 2009b). Proposals need to respond to the specific terms set out in the SBIR annual solicitation (NIST, 2009b). Although an emphasis on field technologies that are useful in developing countries would be a departure from the Department of Commerce's charge of promoting American industry, there is enough of a shared stake in drug safety that they might consider a SIBR solicitation for innovative technologies to detect poor-quality drugs.

There is considerable scope for innovative research in drug detection

TABLE 6–1 Techniques for Detecting Poor-Quality Drugs

Technique	Good for	Cost
Visual inspection	Detecting unsophisticated falsified drugs: wrong color, size, shape, packaging, etc.	Inexpensive
Packaging technologies: holograms, barcodes, pedigrees	Detecting fake packaging	Inexpensive
Physical and bulk property testing (e.g., density, solubility, refractive index)	Varies, but usually identifying the active ingredient	Varies
Colorimetry	Identifying functional groups in ingredients, relative amount of active ingredients	Inexpensive
Disintegration tests	Determining whether product will disintegrate correctly	Inexpensive
Dissolution tests	Determining whether product will dissolve correctly, a measure of bioavailability	Expensive
Thin layer chromatography (TLC)	Identifying active ingredients, determining amount of active ingredients	Inexpensive

and analysis. All of the methods described in this chapter, for example, are relevant to small molecules, but hormones, oral contraceptives, low-dose vaccines, and biologics are also vulnerable to quality failures, failures that are much harder to detect. Even the existing technologies to detect falsified and substandard small molecules could be improved. For example, the Minilab, a useful and elegant kit, can test only 63 drugs (GPHF, 2012b). The Global Pharma Health Fund should expand this inventory; the WHO should help identify which products are the first priority for inclusion.

Similarly, expansion of the Raman active ingredient database would make handheld Raman spectrometers more useful in detecting falsified drugs. All drug detection technologies would be more powerful if there were a full authentication database with information about drug color, shape, size, weight, Raman and near-infrared reflectance, and a TLC procedure for assay. Drug companies may balk at releasing this information, but the committee believes that stringent regulatory agencies should require it. Sharing all drug authentication information in a drug quality library would vastly improve the power of existing drug detection technologies.

Level of Training	Speed	Used in Field?	Example
Low	Fast	Yes	A sample of falsified Viagra in Hungary was pink instead of the correct blue color. Further analysis revealed that the tablets contained 15 mg amphetamine instead of the correct active ingredient (U.S. Drug Enforcement Administration Office of Forensic Sciences, 2004).
Low	Fast	Yes	mPedigree developed scratch-off codes for prescription boxes. Consumers text the code to a phone number and receive a confirmation—or not—that their product is genuine (Sharma, 2011).
Low-high	Varies	Varies	An artesunate extraction should significantly lower the pH of water, and some falsified versions do not do this (Newton et al., 2006).
Low	Fast	Yes	Fast Red TR dye turns yellow in the presence of artesunate (Green et al., 2001).
Low	Fast	Yes	Close to 12% of drugs sampled from Delhi in a study of drug quality in India failed disintegration testing (Bate et al., 2009b).
High	Slow	No	In one study, 14% of drugs that initially passed dissolution testing subsequently failed, rendering them substandard, after 6 months of storage in tropical conditions (Kayumba et al., 2004).
Low-moderate	Fast	Yes	Detected substandard tuberculosis drugs with the wrong amount of active ingredient in Botswana (Kenyon et al., 1999).

continued

TABLE 6–1 *Continued*

Technique	Good for	Cost
Gas chromatography (GC) with appropriate detection technology	Identifying and quantifying volatile active ingredients, residual solvents, volatile contaminants, undeclared ingredients	Expensive
High-performance liquid chromatography (HPLC) with appropriate detection technology	Identifying and quantifying active ingredients, impurities and various nonvolatile components	Moderate
Mid-infrared (IR) spectroscopy	Identifying active ingredients and excipients; some techniques can analyze packaging and tablet coatings	Moderate-expensive
Near-infrared spectroscopy	Identifying and quantifying active ingredients, excipients	Moderate-expensive
Nuclear magnetic resonance (NMR) spectroscopy	Identifying and quantifying active ingredients and excipients; provides detailed structural information	Expensive
Raman spectroscopy (conventional)	Identifying active ingredients and excipients, relative concentration of ingredients; identifying tablet coating composition	Moderate-expensive
Raman spectroscopy (portable)	Same as conventional Raman spectroscopy, but can be less reliable	Moderate
Mass spectrometry (MS)	Identifying active ingredients, excipients, undeclared ingredients, impurities	Expensive
Direct mass spectrometry (DART-MS, DESI-MS)	Identifying active ingredients, excipients, undeclared ingredients, detecting analogues	Expensive
Gas chromatography-mass spectrometry (GC-MS)	Volatile active ingredients, residual solvents, volatile contaminants, undeclared ingredients	Expensive
High-performance liquid chromatography-mass spectrometry (HPLC-MS)	Identifying and quantifying active ingredients, excipients, undeclared ingredients, impurities	Expensive

Level of Training	Speed	Used in Field?	Example
High	Slow	No	Organic volatile impurities detected by GC can help link different batches of falsified drugs back to common manufacturers (Mulligan et al., 1996).
Moderate-high	Slow	No	Common antimalarials chloroquine, quinine, and mefloquine produce different peaks in an HPLC chromatogram (Gaudiano et al., 2006).
Moderate	Fast	No	Artemisinin and artemether produce different IR spectra. Artemisinin is sometimes substituted for its derivatives, such as artemether, in falsified products (Kaur et al., 2010).
Moderate	Fast	Yes	Was able to distinguish real from falsified artesunate tablets with 100% accuracy in an analysis of samples from Southeast Asia (Dowell et al., 2008).
High	Slow	No	Diffusion-ordered proton NMR spectroscopy identified incorrect active ingredients in a study of falsified artesunate samples and was able to detect excipient ingredients that two mass spectrometric techniques could not (Nyadong et al., 2009).
Moderate	Fast	No	Close examination of Raman spectra comparing a suspected falsified drug to a real sample revealed a slight discrepancy due to differences in tablet coating (Witkowski, 2005).
Low	Fast	Yes	Falsified artesunate samples did not produce the strong fluorescence characteristic of artesunate when scanned with a portable device (Ricci et al., 2008).
High	Slow	No	Falsified halofantrine containing a sulphonamide antibiotic detected with MS (Wolff et al., 2003).
Moderate	Fast	No	Detected falsified artesunate that contained paracetamol (Martino et al., 2010).
High	Slow	No	Detected falsified Captagon tablets containing alternative stimulants (Alabdalla, 2005).
High	Slow	No	Distinguished between falsified and genuine samples of Nigerian dihydroartemisinin (Kaur et al., 2010).

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7

An International Code of Practice for Falsified and Substandard Medicines

Ensuring a safe, reliable drug supply is ultimately a matter for individual countries. To this end, every nation has four main responsibilities: regulating the responsible manufacture of safe and effective medicines; preventing falsified and substandard drugs from entering the market; detecting them when they do; and punishing those who knowingly manufacture and trade them. Executing these responsibilities requires strong national systems for drug regulation, surveillance, and law enforcement. Governments must work with key stakeholders in industry, professional associations, and civil society to protect the drug supply.

However, no country acting alone can protect its citizens from falsified and substandard medicines. The problem, as seen throughout this report, is international, fueled by international trade and telecommunications. Crime and easy money are powerful forces driving the illegitimate medicines business. Its perpetrators gravitate to countries where surveillance, regulation, and law enforcement are the weakest. They take advantage of international manufacturing and trade to produce and sell their products in the global market.

The interconnectedness of modern manufacturing systems makes the "quality and safety of goods . . . that travel in international commerce" (Gostin and Taylor, 2008, p. 54) a global public health concern. A coherent system of global governance founded on diplomacy and international cooperation can improve product safety and protect health around the world (Gostin and Taylor, 2008). This will require cooperation among countries, among agencies within governments, and among consumers, manufacturers, professional associations, and civil society groups.

This chapter discusses the global governance tools available to fight the public health problem of falsified and substandard drugs. An emphasis on the public health risks of illegitimate drugs is central to framing this problem; protecting drug companies' proprietary interests is not. In the past, disagreements about the overlap between public health protection and intellectual property guarantees have crippled international discussion on drug safety. Any global governance process will need to focus on public health, a goal all parties can support and come to consensus around.

Global governance includes hard law, such as treaties, and soft law, such as resolutions, declarations, memorandums of understanding, and codes of practice (Gostin, 2013). The committee does not believe that the time is ripe for hard-law solutions. If countries or regions wish to negotiate a treaty on falsified and substandard drugs, then they should do so, but international soft law may be a more practical short-term solution to the problem. A soft-law solution could encourage international momentum for drug regulation, surveillance, and law enforcement. It would also build trust among stakeholders and pave the way for a future hard-law solution if necessary.

Two treaty processes already under way relate to the problem of substandard and falsified medicines. The Council of Europe's Medicrime Convention (officially, "the Convention on the counterfeiting[1] of medical products[2] and similar crimes involving threats to public health") is a multilateral treaty intended to prevent the public health threats of illegitimate medicines (Council of Europe, 2011). The convention aims to make crimes of drug adulteration and of the intentional manufacture, supply, or trade in illegitimate medicines or ingredients, and their accessories (Council of Europe, 2011). Other criminal offenses under Medicrime include tampering with the drug pedigree or making false drug documents; putting an unauthorized drug on the market; and intentionally aiding or abetting a criminal in one of the named offenses (Council of Europe, 2011). Medicrime also gives terms for protecting victims, including victim's rights to compensation from perpetrators, and for international cooperation in investigation, extradition, and mutual legal assistance (Council of Europe, 2011). By December 2012, 22 countries had signed the convention, but only Ukraine had ratified it (Council of Europe, 2012). Medicrime will not come into force until five countries ratify it, including three Council of Europe members (Council of Europe, 2011).

Critics of the convention see in Medicrime an attempt to treat routine

[1] The Medicrime Convention defines a counterfeit as a false representation of identity or source (Council of Europe, 2011).

[2] The Medicrime Convention defines a medical product as human and veterinary medicines and medical devices (Council of Europe, 2011).

quality control errors as crimes (Attaran and Bate, 2010). And, though Susanne Keitel, the director of the European Directorate for the Quality of Medicines, explained to the committee in March that the Medicrime Convention does not cover infringement of intellectual property rights, some see hostility to generics companies in the treaty (Attaran and Bate, 2010). This impression is fueled by the recent memory of European Union (EU) customs officials seizing as counterfeit generic drug shipments produced in India and bound for Africa or Latin America (EUbusiness, 2010; Reuters, 2011).

The Anti-Counterfeiting Trade Agreement (ACTA) is the other treaty relevant to falsified medicines. ACTA sets international standards for intellectual property protection and creates a regime outside of the World Trade Organization (WTO) and the World Intellectual Property Organization (WIPO) to protect intellectual property (Ilias, 2012). Eight countries[3] signed ACTA in October 2011, but Japan is the only country that has formally ratified the treaty (MOFA of Japan, 2012; USTR, 2011). ACTA will come into force only when six countries ratify it (USTR, 2011).

As Chapter 1 explains, this report is not concerned with intellectual property rights. The committee believes that the real or perceived mixing of public health and intellectual property concerns only holds back action on the problem of falsified and substandard drugs.

THE ROLE OF THE WHO

Protecting public health is the goal of the proposed code of practice on falsified and substandard drugs. Therefore, the World Health Organization (WHO) is the natural home for the negotiation, development, and adoption of the code. Article 2 of the WHO Constitution authorizes the organization, "to act as the directing and coordinating authority on international health work."[4] To this end, the WHO Constitution also grants extensive normative powers to World Health Assembly (WHA), the governing body of the WHO. The WHA's jobs include determining the organization's policies and budget, appointing the Director-General, directing the Executive Board on areas for study or action, inviting other organizations to participate in WHO activities, and maintaining agreements with the United Nations.[5] The assembly also has the authority to recommend actions to members and

[3] Australia, Canada, Japan, Morocco, New Zealand, Singapore, South Korea, and the United States have signed ACTA (USTR, 2011).

[4] World Health Organization, Basic Documents, Constitution of the World Health Organization, 45th ed., Supplement, October 2006. Chapter II, Article 2(a).

[5] World Health Organization, Basic Documents, Constitution of the World Health Organization, 45th ed., Supplement, October 2006. Chapter V, Article 18(a), (c), (d), (f), (h), (j).

Key Findings and Conclusions

- The political climate is not conducive to a hardlaw, such as a multilateral treaty, against falsified and substandard drugs.
- A code of practice is a soft-law solution that would give member states clear, consistent guidelines and benchmarks for their work against falsified and substandard drugs.
- The WHO should lead in the development of a code of practice on falsified and substandard drugs, in consultation with the World Customs Organization (WCO), the United Nations Office on Drugs and Crime (UNODC), and other stakeholders.

to require members to give yearly reports on action taken to comply with recommendations.[6]

This report makes clear that substandard and falsified medicines are an international problem. There is a precedent for the WHO establishing international codes on problems of global public health consequence. Concern about the marketing of infant formula to new mothers led to the 1981 WHO and Unicef *International Code of Marketing of Breast-Milk Substitutes* (WHO, 1981). In 2010, the WHO responded to the problem of international health worker migration with *The Global Code of Practice on the International Recruitment of Health Personnel* (WHO, 2010). The codes were possible because of WHO leadership and an open, consultative, deliberation process. The committee believes that a similar process, led by the WHO, will be essential to international action against illegitimate drugs.

The WHO is also the international leader in the current discussion about substandard and falsified drugs. In November 2012, WHO member states met in Argentina as part of a new effort to collaborate on illegitimate medical products (WHO, 2012b). In her opening remarks, Director-General Margaret Chan reiterated the organization's commitment to working against harmful products in the drug supply and promoting the availability of good-quality medicines around the world (Chan, 2012).

Engaging Stakeholders

In developing the proposed code of practice, the WHO should engage all major stakeholders; the inclusion of scientific experts and civil society

[6] World Health Organization, Basic Documents, Constitution of the World Health Organization, 45th ed., Supplement, October 2006. Chapter V, Article 20, Article 23.

groups is essential. The WHO Essential Medicines division can bring great technical depth to the discussion, especially the public health aspects of the problem. Because the problem has legal dimensions, it will also be crucial to include experts in law enforcement, criminal justice, and customs. In order to assure the proper range of expertise in the drafting of the proposed code of practice, the committee recommends that the WHO work with the UNODC and the WCO.

The UNODC helps member states fight organized crime, trafficking, corruption, and terrorism (UNODC, 2012a). Its previous work has described the trade in illegitimate medicines as the business of terrorist organizations and criminal cartels (UNODC, 2009, 2011, 2012b). The agency's 2012-2015 strategy emphasizes that responding to transnational, organized crime is a priority, and it highlights their work against new kinds of drug trafficking (UN, 2012). Contributing to the law enforcement and criminal justice sections of an international code on falsified and substandard medicines would draw on the agency's strengths and complement the goals set out in its 3-year strategy.

The WCO, the only international organization dedicated to policing flows of goods into and out of countries, is the other stakeholder organization that should contribute to the proposed code. The WCO works on supply chain security and on the harmonization of simplified customs procedures (WCO, 2012a). National customs offices are under pressure to facilitate international trade and to monitor the safety of products entering the country; they have a unique understanding of the circumstances through which illegitimate medicines enter commerce. The inclusion of the WCO in the development of an international code on falsified and substandard drugs could help ensure the code's validity to stakeholders in customs.

The committee recognizes that some stakeholders might object to the inclusion of the WCO in this process, given the organization's professed commitment to protecting intellectual property rights (WCO, 2012b). Monitoring the trade in illegitimate medicines and enforcing laws against them depend on customs bureaus, however. Failing to include them in the development of the code would risk its being unacceptable or impractical for customs officers, one of the main groups that would need to adhere to it. While some stakeholders might not approve of the WCO, the committee sees no value in excluding them from the discussion.

Global governance for health increasingly requires health organizations such as the WHO to work with other international agencies. There is precedent for the WHO's forming partnerships in the development of a code of practice. The WHO and Unicef collaborated on the *International Code of Marketing of Breast-Milk Substitutes*, and, since its release in 1981, 84 countries have enacted legislation implementing all or many of

its provisions (Unicef, 2012; WHO, 1981). Unicef continues to work with legislators and lawyers to implement maternity protection laws in more countries (Unicef, 2012). Given the clear relationship between maternal and child health and Unicef's mission, it was only appropriate for the WHO to engage this organization. Similarly, a partnership with the UNODC and WCO would benefit the development and implementation of the proposed code of practice.

Recommendation 7-1: The World Health Assembly, in partnership with the United Nations Office on Drugs and Crime and the World Customs Organization, and in consultation with major stakeholders, should institute an inclusive, transparent process for developing a code of practice on the global problem of falsified and substandard medicines. The code should include guidelines on surveillance, regulation, and law enforcement, empowering states and the international community to prevent and respond to drug quality problems.

CONTENT OF THE CODE

The code will not be credible unless it is developed through a fair and inclusive process; such processes take time. At a minimum, however, the committee recommends that the process give some attention to international surveillance, drug regulation, and law enforcement as main areas in which to give guidance.

International Surveillance

As Chapter 3 explains, surveillance for substandard and falsified drugs is uncoordinated, largely voluntary, and highly variable. The modern drug

Key Findings and Conclusions

- The international surveillance component of the code of practice should provide guidelines on how to develop a surveillance system for falsified and substandard drugs and how to link it to routine pharmacovigilance.
- The code should recommend guidelines, minimum standards, and benchmarks for medicines regulation.
- The code of practice should provide guidance on how to investigate and punish pharmaceutical crimes, suggest standard minimum punishments for different crimes, and establish common definitions for various criminal acts.

supply chain involves many countries; therefore, drug surveillance should be a coordinated, global effort. International surveillance is necessary to define the magnitude of the problem and to identify priority areas for action.

The sections of the code that discuss surveillance should give guidance on how to set up routine drug quality surveillance and how to make strategic choices about which drugs to monitor in the most vulnerable regions. Once routine surveillance systems are running, data gleaned from them will inform some of these choices in an iterative process. It may be necessary to use active surveillance methods for some high-risk drugs and passive surveillance for others. The code might also recommend how to choose and manage key sentinel surveillance sites. The guidelines should also explain how to tie monitoring for falsified and substandard drugs to routine pharmacovigilance and how to link surveillance with response.

Drug surveillance also requires laboratories for quality testing. There are not sufficient drug-quality laboratories in most low- and middle-income countries to support the regulatory agencies' routine needs (IOM, 2012). And, as Chapter 6 explains, these assays are expensive; running even minimal tests could quickly bankrupt a small county's annual drug testing budget. The code should suggest ways to accommodate the added burden that surveillance will place on drug quality laboratories. There may be room for universities to take on more testing or for donors to fund dedicated, regional drug surveillance laboratories. The use of minilabs and hand-held detection technologies could also alleviate the added strain surveillance testing will place on drug quality laboratories.

Building surveillance also requires building a workforce dedicated to data analysis and the prompt dissemination of public alerts when necessary. Therefore, using surveillance data effectively requires a strong medicines regulatory system. Guidelines on surveillance for falsified and substandard drugs will depend on commensurate guidelines for the regulation of medicines.

Medicines Regulation

The proposed code of practice should give guidelines on the quality, safety, and efficacy of medicines that all countries can work toward. The code could suggest national minimum standards for licensing of importers, distributors, and wholesalers and guidelines on retail and dispensing of medicines. The WHO has already collected most of this information; the Medicines Regulatory Package will be a useful reference on how to organize regulatory authorities and monitor their performance (WHO, 2011).

The code should direct countries to enact comprehensive medicines legislation that provides for all the drug regulatory functions, including the licensing of manufacturers and distributors, the issuing of market au-

thorization, the inspection and surveillance of the drug distribution chain, and the monitoring of medicines on the market (Rägo and Santoso, 2008).

The code should also give guidance on harmonization and mutual recognition. Having consistent requirements eases the regulatory burden on industry. Especially in small countries, harmonization allows regulators to make efficient use of their limited labor. The code might recommend opportunities for regulatory agencies in small countries to base their decisions on internationally accepted criteria. The regulatory agencies of Canada, New Zealand, Singapore, and Switzerland, for example, make more efficient use of their staff by accepting new chemical entity data from larger regulatory agencies (ICDRA, 2010; Jessamine, 2010).

The code might support the work the Pharmaceutical Inspection Cooperation Scheme has begun. The Pharmaceutical Inspection Convention and the Pharmaceutical Co-operation Scheme, known jointly as PIC/S, work to advance mutual confidence, training, and information exchange among 43 participating regulatory agencies (PIC/S, 2012b, 2013). PIC/S trains inspectors from around the world in pharmaceutical inspections; its trainings and publications promote harmonized understanding of good distribution and manufacturing practices (PIC/S, 2012c,d).

Efficient staffing of the regulatory authority depends on sustainable financing. The code could suggest methods for governments to ensure sustainable financing for their regulatory authorities. Most regulatory authorities run off public money or market authorization fees; many face an additional dilemma in soliciting user fees from the pharmaceutical industry (Abdul-Rahman, 1996). The code might address this problem and give guidelines on an appropriate financial relationship between the pharmaceutical industry and the drugs regulatory authority. A frank public discussion of this question might have an added benefit of encouraging investment in regulatory systems in developing countries. This includes investing in the training and credentialing of the professional workforce needed to run a regulatory system.

The code of practice could also lead to the development of accepted good regulatory practices, and tools regulators can use to benchmark their performance. The WHO is the ideal organization to lead the development of good regulatory practices because of its technical depth and experience in medicines regulation. The WHO has convening power to bring regulatory agencies together; its International Conference of Drug Regulatory Authorities brings regulators together to discuss common challenges and opportunities for collaboration (WHO, 2012a). The development of good regulatory practices could also draw on the work that the International Conference on Harmonisation and the forum for Asia-Pacific Economic Cooperation have done to the same end (Lourenco, 2008; Uyama, 2011).

Law Enforcement

Guidelines for surveillance and drug regulation will be central to a code of practice on substandard and falsified drugs. This report makes clear, however, that the problem cannot be solved without input from law enforcement, a broad category that includes disparate agencies with limited budgets and competing priorities.

The nature of pharmaceutical crimes and the constraints on law enforcement agencies pose challenges to prosecuting and punishing offenders. The illegitimate drug business is a global industry that mirrors legitimate business in many ways: it sources materials from around the world and bases manufacturing in countries with the cheapest labor and most favorable regulatory regimes. Criminals and unscrupulous manufacturers use the internet to identify suppliers and customers. They may also sell drugs over the internet, on the black market, or even through legitimate distribution channels. Thorough investigation and successful prosecution of those responsible is difficult and expensive because of clandestine manufacturing and distribution networks.

Pharmaceutical crime covers a spectrum of low-risk, high-reward offenses. Many countries have not enacted laws making these acts crimes or set out terms for international cooperation on investigations (Attaran et al., 2011). The code of practice on falsified and substandard medicines could give guidelines on how to investigate and punish the illegitimate medicines trade, as well as standard minimum punishments for different crimes. The code could also establish common definitions for different criminal acts such as the manufacture of an illegitimate drug, the unauthorized reuse of packaging, tampering with any documents or receipts necessary to recreate the chain of custody, and knowingly selling or distributing an illegitimate product.

A code of practice would build momentum for international cooperation on the investigation of pharmaceutical crimes. The national police agencies' authority stops at the border. Investigating transnational crimes sometimes requires mutual legal assistance treaties (Attaran et al., 2011; Palmer, 2012). Pharmaceutical crimes are particularly time-consuming and expensive to investigate. They put novel demands on the detectives and prosecutors who are expected to work on homicides and other violent crimes. The code of practice could suggest guidelines for police agencies on how to balance priorities. It could also give political cover to police agencies looking to direct more staff time to investigating crimes against the drug supply. The code would also establish guidelines for both choosing the venue to prosecute and the terms for extradition.

Chapter 4 describes how police and customs officers may channel their work against falsified drugs in brief, intense campaigns and not in sus-

tained, coordinated action. The law enforcement guidelines in the proposed code of practice could explain how to integrate action against falsified drugs into daily police work. They would also allow police and prosecutors to make these crimes a priority.

At a minimum, the code should establish definitions for different crimes involving the medicine supply, establish minimum penalties for these crimes, recommend protocols for international cooperation on investigations and extradition, and clarify the role of customs and border police in investigating medicines trafficking. These actions could go a long way in increasing awareness of the gravity of pharmaceutical crime.

Compliance by States and Stakeholders

A code of practice is a voluntary agreement. Countries have no formal, legal obligation to conform. A code of practice can do much to raise awareness and promote harmonized actions among countries. Some recent commentary has suggested that the WHO should exercise more leadership on global health problems (Sridhar and Gostin, 2011). The organization is uniquely poised to convene stakeholders and issue a soft law for addressing this problem. An open and transparent convening process will lay the groundwork for future compliance with the code.

The WHO can also give incentives for compliance and encourage cooperation among nations. Countries that adopt the code should be able to report on their progress and share strategies for overcoming obstacles. The WHO Director-General could then report to the WHA on implementation and potential barriers to compliance. Nongovernmental organizations could also have a useful role in monitoring compliance with the code, perhaps issuing reports on which countries and stakeholder groups make good on their promises (Gostin, 2013).

One likely barrier to action is limited capacity for drug regulation, law enforcement, and surveillance in low- and middle-income countries. The code might suggest incentives, such as funding and technical assistance for implementation, as well guidance on how law enforcement agencies can work together across jurisdictions.

Costs are another important barrier to widespread adaption of the code. The PIC/S funds its activities through membership fees (PIC/S, 2012a). Attendance at conferences and trainings is extra (PIC/S, 2012a). The expense can be a barrier for regulators from poor countries. Furthermore, tracking countries' progress to meeting the code and planning member state activities will take staff time and administrative effort. It may be necessary to establish a WHO secretariat dedicated to the code of practice on falsified and substandard drugs. In this case, the WHA should direct the necessary

funds to WHO for a formal secretariat to organize and administer related activities.

Substandard and falsified drugs are a global problem. It is difficult to accurately measure the burden of the problem, but illegitimate medicines appear in all countries, threatening health and undermining confidence in the medical system. The proposed code of practice will encourage coordinated international monitoring of medicine quality, strong regulatory systems, and the appropriate investigation and punishment of crimes against the drug supply. Prominent international action to protect the drug supply will advance public health around the world.

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Appendix A

Glossary

Active pharmaceutical ingredient (API): Any substance or mixture of substances that is part of a drug (medicinal) product, intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure and function of the body.

Adulteration: The alteration of a product by deliberately adding something not ordinarily a part of it.

Adverse drug reaction: A harmful result of drug therapy that is neither intended nor expected in normal therapeutic use.

Anthelmintic resistance: The ability of worms to survive treatment at the generally effective recommended dose.

Antibiotic: A drug that fights bacterial infections.

Anti-Counterfeiting Trade Agreement (ACTA): An initiative signed on October 1, 2011, by key trading partners to strengthen the international legal framework for effectively combating global proliferation of commercial-scale counterfeiting and piracy. It calls for strong legal frameworks and innovative provisions to deepen international cooperation and to promote strong intellectual property rights enforcement practices.

Anti-infective: A substance that aids the immune system by inhibiting infective microorganisms by destroying their cell wall, slowing their growth, or interfering with DNA synthesis.

Antimalarial: Drugs designed to prevent or cure malaria.

Antimicrobial: A substance that kills or inhibits the growth of microorganisms.

Antimicrobial resistance: The ability of microorganisms that cause disease to withstand attack by antimicrobial medicines.

Antiparasitics: A class of medications that treat parasitic diseases.

Antiretroviral drugs: Drugs used to treat people infected with the human immunodeficiency virus.

Artemisinin: A drug used to treat malaria derived from the *Artemisia Annua* plant family. It and its derivatives are a group of drugs that possess the most rapid action against the disease.

Artemisinin-based combination therapy: A combination of artemisinin or one of its derivatives with an antimalarial drug or drugs of a different class.

Artesunate: An artemisinin-derived drug used in the treatment of malaria.

Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy: A well-established, nondestructive method for determining the chemical composition of materials based on their chemical bonding.

Beta-lactam antibiotics: A broad class of antibiotics, consisting of all antibiotic agents that contain a beta-lactam nucleus in their molecular structure. This includes penicillin derivatives, cephalosporins, monobactams, and carbapenems. Most beta-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics.

Bioavailability: Bioavailability is a subcategory of absorption and is the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100 percent. However, when a medication is administered via other routes (such as orally), its bioavailability generally decreases due to incomplete absorption and first-pass metabolism. Bioavailability is one of

the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for nonintravenous routes of administration.

Bioequivalent: The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents becomes available at the site of drug action, when administered at the same molar dose under similar conditions in an appropriately designed study.

Black market: A market of goods or services that operates outside the formal market, not supported by an established state power.

Blister packet: Perforated packaging used for drugs and other consumer products.

Blockbuster drugs: Popular drugs that generate at least $1 billion in annual sales for the company that creates them.

British Pharmacopoeia: Established in 1864, the British Pharmacopoeia provides authoritative official standards for pharmaceutical substances and medicinal products in the United Kingdom and many other countries that have adopted it.

Bulk property: A property that does not depend on the size or amount of a sample. For example, density is a bulk property because it does not depend on the amount of substance tested. A bulk property may also be called an intensive property.

Central medical store: Primarily found in developing countries, it is the Ministry of Health's procurement arm and national medical store. Central medical stores are generally responsible for the procurement, quality assurance, storage and distribution of drugs, vaccines, disinfectants, dressings, and related medical supplies for government health facilities and some nongovernment organizations.

Chain of custody: A document intended to guarantee the integrity of a drug product along the distribution chain.

Chromatography: A method for separating a mixture into its constituent substances. The separation is based on differential partitioning between a mobile and stationary phase. Subtle differences in a compound's partitioning result in differential retention on the stationary phase, thus effecting

the separation. This method is used to separate mixtures such as drugs for accurate and precise analysis.

Civil liability: The potential responsibility for payment of damages or other court enforcement in a lawsuit.

Colorimetry: The experimental measurement of the amount of color produced by a colorimetric reagent and a sample.

Compounding: The creation of a particular pharmaceutical produce to fit the unique needs to a patient. To do this, compounding pharmacists combine or process appropriate ingredient using various tools. This may be done for medically necessary reasons, such as to change the form of the medication from a solid pill to a liquid, to avoid a nonessential ingredient that the patient is allergic to, or to obtain the exact dose(s) needed of particular active pharmaceutical ingredient(s). It may also be done for more optional reasons, such as adding flavors to a medication or otherwise altering taste or texture.

Compulsory license: Also known as statutory license of mandatory collective management, provides that the owner of a patent or copyright licenses the use of their rights against payment either set by law or determined through some form of arbitration. In essence, under a compulsory license, an individual or company seeking to use another's intellectual property can do so without seeking the rights holder's consent, and pays the rights holder a set fee for the license. The principal requirement for the issues of a compulsory license under TRIPS is that attempts to obtain a license under reasonable commercial terms must have failed over a reasonable period of time. TRIPS also provides that the requirements for a compulsory license may be waived in certain situations, in particular cases of national emergency or extreme urgency or in cases of public noncommercial use.

Contract manufacturing: The manufacturing of a product by an organization or company other than the marketing company.

Convenience sample: A type of nonprobability sampling which involves the sample being drawn from the part of the population that is close to hand. That is, a sample population selected because it is readily available and convenient. The researcher using such a sample cannot scientifically make generalizations about the total population from this sample because it would not be fully representative.

Counterfeit: A drug that bears an unauthorized representation of a registered trademark on a product identical or similar to one for which the trademark is registered.

Crude active ingredients: Chemicals that have not undergone the appropriate purification steps required to meet pharmacopeial standards or manufacturer's dossier requirements.

Degraded: The deterioration of an active pharmaceutical ingredient in a drug. It can be a result of high temperatures exceeding label requirements, resulting in decreased potency and efficacy.

Density: The ratio of an object's mass to its volume.

Developing country: A nation with a low living standard, undeveloped industrial base, and low human development index relative to other countries.

Development bank: A national or regional financial institution designed to provide medium- and long-term capital for productive investment, often accompanied by technical assistance in developing countries.

Diffusion-ordered proton nuclear magnetic resonance spectroscopy: A type of nuclear magnetic resonance spectroscopy that can identify the various types of ingredients in a mixture by taking advantage of differences in molecular mass. It separates the nuclear magnetic resonance signals of different components according to their diffusion coefficient.

Direct ionization: The impulses alpha and beta particles apply to orbital electrons to ionize, or completely remove an electron from an atom following the transfer of energy from a passing charged particle. Specific ionization, the number of ion pairs formed per unit path length for a given type of radiation, is a measure of the intensity of ionization. Because of their double charge and relatively slow velocity, alpha particles have a high specific ionization and a relatively short range in matter (a few centimeters in air and only fractions of a millimeter in tissue). Beta particles have a much lower specific ionization than alpha particles and, generally, a greater range.

Direct-to-pharmacy: A supply chain model where manufacturers sell directly to pharmacies.

Directly Observed Treatment–Short Course (DOTS): The internationally recommended strategy for tuberculosis control. It is a standardized treat-

ment regimen directly observed by health care or community workers. It has been recognized as a highly efficient and cost-effective strategy to control the disease.

Disintegration: The process of breaking up a solid dosage form in water or simulated gastric solution.

Dispensary: A place where medicine or medical or dental treatment is dispensed.

Dissolution: The process by which a substance is dissolved.

Distribution chain: A series of businesses or organizations involved in transporting, storing, and selling goods from the manufacturer to consumers.

Diversion: The unlawful channeling of products from a legitimate, parallel marketed, subsidized supply chain into other, unsubsidized markets.

Doha Declaration: A declaration adapted by World Trade Organization members in 2001. It affirms the right of all countries to protect public health and enhance access to medicines for poor countries.

Drug: A substance used as a medication or in the preparation of medication.

Drug pedigree: A statement of origin that identifies each prior sale, purchase, or trade of a drug, including the date of those transactions and the names and addresses of all parties to them.

Drug potency: The extent to which a drug product contains the specified amount of active ingredient.

Drug resistance: The reduction in effectiveness of a drug in curing a disease or condition due to mutations in the target organism.

Economies of scale: Factors that cause the average cost of production to fall as the volume of output increases.

Efficacy: The ability of a drug to produce the desired therapeutic effect.

Electromagnetic spectrum: The entire range of wavelengths or frequencies of electromagnetic radiation extending from gamma rays to the longest radio waves, including visible light.

Electronic product code: A radio frequency identification code, attached to a product, that contains a wide range of information unique to that item and may include the manufacturer, stock-keeping unit, product information, and batch number. This allows tracking a particular item throughout all stages of the supply chain.

Electrospray ionization-mass spectrometry (ESI-MS): An ionization technique that uses electrical energy to assist the transfer of ions from solution into the gaseous phase before they are subjected to mass spectrometric analysis. This technique is used to ionize small amounts of large or labile molecules such as peptides, proteins, organometallics, and polymers. The multiply charged ions then enter the analyzer. The most obvious feature of an ESI spectrum is that the ions carry multiple charges. This characteristic reduces their mass-to-charge ratio compared to a singly charged species and facilitates obtaining mass spectra for large molecules.

E-pedigree: An electronic record that documents a drug's pedigree.

Epidemiologic transition: A theory that focuses on the complex change in patterns of health and disease and on the interactions between these patterns and their demographic, economic and sociologic determinants and consequences. The transition portion of the theory is concerned with changes in population growth trajectories and composition, especially in the age distribution from younger to older. It also takes into account the changes in patterns of mortality, including increasing life expectancy and reordering of the relative importance of different causes of death.

Excipient: A pharmacologically inactive substance used along with the active pharmaceutical ingredients in the formulation of a medication.

Expert review panel: A panel of independent experts, who review the potential risks and benefits associated with the use of finished pharmaceutical products or diagnostic products. The panel makes recommendations as to whether the products may be procured.

Fake: Widely used as a synonym for *falsified* in this report and by other scholars.

Falsified: A drug that falsely represents a product's identity or source or both.

Finished product: A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labeling.

Forensic chemistry: A field of chemistry focused on analyzing substances in support of law enforcement.

Formal market: An official market, as recognized by a government.

Formulary: A list of medications approved under a particular insurance policy. A national formulary contains a lists of medicines that are approved for prescription throughout the country, indicating which products are interchangeable. It includes key information on the composition, description, selection, prescribing, dispensing, and administration of medicines. Those drugs considered less suitable for prescribing are clearly identified.

Formulation: A mixture of substances prepared according to a specific formula; included in a capsule, a pill, a tablet, or an emulsion.

Fraudulent: A product claiming particular qualities with intent to deceive.

Friability: A measure of the ability of a solid substance to be reduced to smaller pieces with tumbling.

Fourier-transform infrared spectrometry: A measurement technique whereby infrared spectra are collected based on nondispersive spectral measurements. As with all other infrared spectral measurements, this technique can identify unknown materials, determine the quality or consistency of a sample, and determine the amount of components in a mixture.

Gas chromatography: A common type of chromatography used in analytical chemistry for separating and analyzing compounds that can be vaporized without decomposition. It is typically used to test the purity of a particular substance or separate different components of a mixture. In some situations, gas chromatography may help identify a compound.

Gas chromatography-mass spectrometer (GC-MS): A tool used for the identification and quantitation of volatile and semi-volatile organic compounds in mixtures. The GC-MS consists of two parts: the gas chromatograph and the mass spectrometer. The gas chromatograph separates the molecules in the sample, allowing some of them to pass into the mass spectrometer more rapidly than others. When the molecules move into the mass spectrometer, they are ionized into fragments and each molecule is identified based on

mass and charge. The GC-MS spectrometer helps separate and determine the individual elements and molecules in a sample. It is used for the quantitation of drugs and provides forensic investigators the ability to identify individual substances that may be found within a very small test sample.

Good manufacturing practices: A system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

Gray market: A supply channel that is unofficial, unauthorized, or unintended by the original manufacturer.

Hard currency: A globally traded currency that is expected to serve as a reliable and stable store of value.

Herd immunity: A situation in which a sufficient proportion of a population is immune to an infectious disease (through vaccination or prior illness) to make its spread from person to person unlikely. Even individuals not vaccinated (such as newborns and those with chronic illnesses) are offered some protection because the disease has little opportunity to spread within the community.

High-performance liquid chromatography (HPLC): A technique used to separate a mixture of compounds to identify, quantify, and purify the individual components of the mixture. This technique relies on pumps to pass a pressurized liquid and a sample mixture through a column filled with a sorbent, leading to the separation of the sample components. The active component of the column, the stationary sorbent, is typically a granular material made of solid particles, 2-50 micrometers in size, which may be coated. The components of the sample mixture are separated from each other due to partitioning differences with the sorbent particles. The pressurized liquid is typically a mixture of solvents (e.g., water, acetonitrile, or methanol) and is referred to as the mobile phase. Its composition and temperature play a major role in the separation process by influencing the partitioning between sample components and stationary sorbent. HPLC is one of the most powerful tools in analytical chemistry. Depending on the detection system and stationary phase used, it has the ability to separate, identify, and quantitate compounds present in any sample that can be dissolved in a liquid. Compounds in trace concentrations as low as parts per trillion can be separated and with appropriate detectors may be identified using this technique. HPLC can be, and has been, applied to numerous

samples such as pharmaceuticals, food, nutraceuticals, cosmetics, environmental matrices, forensic samples, and industrial chemicals.

Illegal: Not authorized by law.

Illegitimate: Illegal drugs not in accordance with accepted standards. Used in this report and by some scholars as a parent category for falsified and substandard drugs.

Information asymmetry: Condition in which at least some relevant information is known to some but not all parties in a transaction. Information asymmetry causes markets to become inefficient, since all the market participants do not have access to the information they need for their decision making processes.

Infrared spectroscopy: The spectroscopy that deals with the infrared region of the electromagnetic spectrum, that is, light with a longer wavelength and lower frequency than visible light. It covers a range of techniques, mostly based on absorption spectroscopy. As with all spectroscopic techniques, it can be used to identify and study chemicals. A common laboratory instrument that uses this technique is a Fourier transform infrared (FTIR) spectrometer.

Infrastructure: The basic physical and organizational structures needed or the operation of a society or enterprise, or the services and facilities necessary for an economy to function. It can be generally defined as the set of interconnected structural elements that provide the framework supporting an entire structure of development. It is an important term for judging a country or region's development. The term typically refers to the technical structures that support a society, such as roads, bridges, water supply, sewers, electrical grids, telecommunications, and so forth.

Innovator drug: Generally the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety, and quality according to requirements at the time of the authorization.

Intellectual property: The ownership of creations of the mind. It includes inventions, literary and artistic works, symbols, names, images, and designs used in commerce.

Intermediaries: The parties involved in the distribution of pharmaceuticals. They include distributers, stockists, and retailers.

International nonproprietary name: The official nonproprietary or generic name given to a pharmaceutical substance, as designated by WHO.

International pharmacopoeia: A pharmacopoeia published by the WHO, established in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and with other specialists, intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements.

Lifestyle drug: A term commonly applied to medications that treat non-life-threatening and nonpainful conditions such as baldness, impotence, wrinkles, erectile dysfunction, or acne, which the speaker perceives as either not medical problems at all or as minor medical conditions relative to others.

Linear barcode: One-dimensional barcodes made up of lines and spaces of various widths, creating specific patterns. These patterns represent stock-keeping unit numbers and batch numbers, which can be easily and quickly read by computer scanners.

Low- and middle-income countries: Countries with a gross national income per capita of less than $12,475.

Manufacturing dossier: An entire collection of records and documents that a manufacturer holds for a particular product, which is generally submitted to a regulatory authority as part of a marketing authorization request.

Marginal cost: The change in total cost that arises when the quantity produced changes by one unit.

Market authorization: An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after a satisfactory evaluation for safety, efficacy, and quality.

Mass spectrometer: An instrument used to measure the precise masses and relative amounts of atomic and molecular ions. In order to measure the characteristics of individual molecules, a mass spectrometer converts them to ions so that they can move and be manipulated by external electric and magnetic fields. The molecules of interest are first introduced into the ionization source of the mass spectrometer, where they are first ionized to acquire positive or negative charges. The ions then travel through the mass analyzer and arrive at different parts of the detector according to their mass-to-charge ratio. After the ions make contact with the detector, usable

signals are generated and recorded by a computer system. The computer displays the signals graphically as a mass spectrum showing the relative abundance of the signals according to their mass-to-charge ratio.

Mass spectrometry: An analytical technique that measures the mass-to-charge ratio of charged particles. It can provide both qualitative (structure) and quantitative (molecular mass or concentration) information on analyte molecules after their conversion to ions. This technique is used for determining masses of particles, for determining the elemental composition of a sample or molecule, and for elucidating the chemical structures of molecules, such as peptides and other chemical compounds.

Medicine: A substance or preparation used in treating a disease.

Medicines registration: A system that subjects all pharmaceutical products to premarketing evaluation, marketing authorization, and postmarketing review to ensure that they conform to required standards or quality, safety, and efficacy established by national authorities. The outcome of the medicines registration process is the issuance or the denial of a pharmaceutical product marketing authorization or license.

Medicrime Convention: The first international treaty established by the Council of Europe against counterfeit medical products and similar crimes involving threats to public health. The Convention makes it an offense to manufacture counterfeit medical products; supply, offer to supply, and traffic counterfeit medical products; falsify documents; manufacture or supply medicinal products without proper authorization; and market medical devices that do not comply with conformity requirements.

Microfluidics: The science and technology of systems that process or manipulate small amounts of fluids, using channels with dimensions of tens to hundreds of micrometers.

Microscopy: The technical field of using microscopes to examine samples and objects that cannot be seen with the unaided eye.

Monograph: A written set of assessment methods and standards that are used to define an acceptable or compliant article (e.g., drug substance, drug product, excipient, or food chemical). Monographs are used to help control the quality of pharmaceutical, dietary supplement, and food ingredient products.

Near-infrared reflectance spectroscopy: An analytical technique used for chemical analyses. It may be used to identify or quantify organic compounds by measuring the absorption of near infrared light by chemical bonds in organic materials.

Nonprobability sample: Also called a nonrandom sample, wherein the selected units have an unknown probability of being selected. Nonprobability samples cannot be used to infer from the sample to the general population. Any generalizations obtained from a nonprobability sample must be filtered through one's knowledge of the topic being studied.

Nosocomial infections: An infection whose development is favored by a hospital environment, such as one acquired by a patient during a hospital visit or one developing among hospital staff. Such infections include fungal and bacterial infections and are aggravated by the reduced resistance of individual patients.

Nuclear magnetic resonance (NMR) spectroscopy: A technique that uses radiofrequency radiation to induce transitions between different nuclear spin states of samples in a magnetic field. NMR spectroscopy can be used for quantitative measurements, but it is most useful for determining a compound's unique structure and identifying the carbon-hydrogen framework of an organic compound.

OECD countries: Thirty-four countries that signed the Convention on the Organisation for Economic Co-operation and Development. They are Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States.

Opportunity cost: The cost of an action measured in terms of the value of the next best alternative action. For example, if capital is used for one purpose, the opportunity cost is the value of the next best purpose the capital could have been invested in.

Osmolarity: The number of osmoles or particles of solute per liter of solution.

Parallel importation: The importation of a product without the permission of the intellectual property owner. Parallel imports are imports of a patented or trademarked product from a country where it is already marketed.

Patent: A set of exclusive rights granted to an inventor or assignee for a limited period of time in exchange for the public disclosure of the invention.

Patent infringement: A violation of the rights secured by a patent.

Pathogen: A bacterium, virus, or other microorganism that can cause disease.

pH: The degree of acidity in a solvent.

Pharmaceutical: A drug with medicinal property.

Pharmaceutical crime: Involves the manufacture, trade and distribution of fake, stolen or illicit medicines and medical devices. It encompasses the counterfeiting and falsification of medical products and their packaging and associated documentation, as well as theft, fraud, illicit diversion, smuggling, trafficking, the illegal trade of medical products, and the money laundering associated with it.

Pharmacist: A person who is licensed to prepare, sell, dispense drugs and compounds, and write prescriptions. They are also referred to as chemists or druggists.

Pharmacopeia: A compilation of monographs that define quality assessment and requirements for acceptable products and the preparation of compound medicines. Compliance with it generally is mandated by the laws of a sovereign state, and it is published by the authority of a government or a medical or pharmaceutical society.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

Postmarket surveillance: The process by which a drug's safety and quality is monitored on an ongoing basis after it is approved.

Price elasticity: The responsiveness, or elasticity, of the quantity demanded of a good or service to a change in its price.

Primary packaging: Packaging in direct contact with the product, intended to protect one or more items and, if needed, to keep it sterile until use.

Procurement: The process of purchasing or otherwise acquiring any pharmaceutical product, vaccine, or nutraceutical for human use.

Procurement agency: Any organization purchasing or otherwise acquiring any pharmaceutical product, vaccine, or nutraceutical for human use.

Quality: The suitability of either an active pharmaceutical ingredient or a pharmaceutical product for its intended use. This term includes such attributes as identity, strength, and purity.

Quality assurance: A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. With regard to pharmaceuticals, quality assurance can be divided into five major areas: development, quality control, production, distribution, and storage.

Quality control: The sampling, specification, testing, organization, documentation, and release procedures that ensure the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

Quality-control laboratory: A laboratory capable of testing product quality.

Radio frequency identification (RFID): A wireless non-contact system that uses radio frequency electromagnetic fields to transfer data from a tag attached to an object, for the purposes of automatic identification and tracking.

Raman spectroscopy: A technique used to observe vibrational, rotational, and other low-frequency modes in a system. It relies on inelastic scattering of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range. The laser light interacts with molecular vibrations, phonons or other excitations in the system, resulting in the energy of the laser photons being shifted up or down. The shift in energy gives information about the vibrational modes in the system.

Reflectance: The measure of the proportion of light or other radiation striking a surface that is reflected off it.

Reflectance spectroscopy: A spectroscopic technique that measures the unabsorbed portion of a beam of light that is shone on the surface of a material, such as a drug product. Reflectance spectroscopy is used for samples that are difficult or inconvenient to analyze by transmission techniques. The

samples can usually be analyzed as is without the need for preparation or modification, but the radiation absorbed is generally limited to the surface or a very limited depth of the sample.

Refractive index: The measurement of the bending of a ray of light as it passes from one medium into another.

Salting: The process by which legitimate and fake drugs are mixed at wholesale.

Sampling frame: A list or other device used to define a researcher's population of interest. It defines a set of elements from which a researcher can select a sample of the target population.

Secondary ion mass spectrometry (SIMS): A technique used in materials science and surface science to analyze the composition of solid surfaces and thin films. This technique sputters the surface of a specimen with a focused primary ion beam and collects and analyzes ejected secondary ions. The mass-to-charge ratios of these secondary ions are measured with a mass spectrometer to determine the elemental, isotopic, or molecular composition of the surface. Due to the large variation in ionization probabilities among different materials, SIMS is generally considered to be a qualitative technique, although quantitation is possible with the use of standards. SIMS is the most sensitive surface analysis technique, with elemental detection limits ranging from parts per million to parts per billion.

Serialization: The assignment and placement of unique markings on a package. Unique codes are placed on each unit packaged, using variable data printers or preprinted labels or cartons, and then read by a vision system. These unique codes are uploaded to an event repository database that can be accessed by various parties, including pharmacists, law enforcement officials, and even consumers after the product is shipped and sold.

Slum: A heavily populated urban area characterized by substandard housing and squalor.

Small- and medium-sized enterprise (SME): Nonsubsidiary, independent firms that employ fewer than a given number of employees. This number varies across national statistical systems. The most frequent upper limit is 250 employees, as in the European Union. However, some countries set the limit at 200 employees, while the United States considers SMEs to include firms with fewer than 500 employees.

Small molecule: The term that describes a low-molecular-weight organic compound.

Solid dose formulation: A mixture of active pharmaceutical ingredients and nondrug components in solid form, such as a pill, tablet, or capsule.

Solubility: The ability of a substance to dissolve and form a homogeneous substance.

Spectrometer: An instrument used for measuring the interaction of light with a substance (e.g., absorption, refraction, reflection, etc.).

Spectrometry: The determination of wavelengths or frequencies in a spectrum.

Spectroscopy: The study of the absorption and emission of light and other radiation by matter.

Standard operating procedure (SOP): Detailed, written instructions to achieve uniformity of the performance of a specific function in pharmaceutical processing and for related clinical studies. The focus is the repeated application of unchanged processes and procedures and its documentation in order to segregate origins, causes and effects.

Stringent regulatory authority: A national drug regulatory authority that participates in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Countries with stringent regulatory agencies include the United States, European Union member states, and Japan, and observers of ICH through legally binding mutual agreements. Observers of ICH include Australia, Canada, Iceland, New Zealand, Norway, and Switzerland.

Substandard: A drug that fails to meet national specifications outlined in an accepted pharmacopeia or in the manufacturer's dossier. Substandard drugs are usually made by legitimate, known manufacturers and are the result of quality system failures.

Supply chain: A system of organizations, people, technology, activities, information, and resources involved in moving a product or service from supplier to customer. Supply chain activities transform natural resources, raw materials, and components into a finished product that is delivered to the end customer.

Surveillance: A key component of epidemiology, it can be defined as the ongoing collection, analysis, interpretation, and dissemination of health-related data. Surveillance is one of a number of methods used by epidemiologists to gather information on a disease.

Tandem mass spectrometry: A technique involving multiple rounds of mass spectrometry, usually separated by some form of molecule fragmentation. For example, one mass analyzer can isolate one peptide from many entering a mass spectrometer. A second mass analyzer then stabilizes the peptide ions while they collide with a gas, causing them to fragment by collision-induced dissociation. A third mass analyzer then sorts the fragments produced from the peptides. An important application using tandem mass spectrometry is in protein identification. Tandem mass spectrometry enables a variety of experimental sequences. Many commercial mass spectrometers are designed to expedite the execution of such routine sequences as selected reaction monitoring (SRM) and precursor ion scanning. In SRM, the first analyzer allows only a single mass through and the second analyzer monitors for multiple user-defined fragment ions. SRM is most often used with scanning instruments where the second mass analysis event is duty cycle limited. These experiments are used to increase specificity of detection of known molecules, notably in pharmacokinetic studies. Precursor ion scanning refers to monitoring for a specific loss from the precursor ion. The first and second mass analyzers scan across the spectrum as partitioned by a user-defined *m/z* value. This experiment is used to detect specific motifs within unknown molecules.

Task shifting: The rational redistribution of tasks among health workforce teams. Specific tasks are moved, where appropriate, from highly qualified health workers to health workers with shorter training and fewer qualifications in order to make more efficient use of the available human resources for health care delivery.

Technology transfer: A process for the transfer of information or technology between a technology supplier and a recipient. It can range from the exchange of technical knowledge through formal documentation, such as a license to exploit a patent, or through technical know-how and assistance in reverse engineering an imitation of a product.

Tendering: The process by which a procurement agency invites potential suppliers to bid for a contract.

Tertiary packaging: Extra packaging intended to protect one or more wrapped items during transport and storage.

Thin layer chromatography (TLC): A chromatography technique used to separate mixtures. TLC is performed on a sheet of glass, plastic, or aluminum foil, which is coated with a thin layer of adsorbent material, usually silica gel, aluminum oxide, or cellulose. This layer of adsorbent is known as the stationary phase. After the sample has been applied to a plate, a solvent or solvent mixture (known as the mobile phase) is drawn up to the plate via capillary action. Because different analytes ascend the TLC plate at different rates depending on their partitioning between the phases, separation is achieved. This technique is used in synthetic chemistry for identifying compounds, determining their purity, and following the progress of a reaction. Specific examples of TLC's applications include drug analysis, analyzing ceramides and fatty acids, detection of pesticides or insecticides in food and water, analyzing the dye composition of fibers in forensics, assaying the radiochemical purity of radiopharmaceuticals, and identification of medicinal plants and their constituents.

Tiered pricing: The concept that different classes of buyers are charged different prices for the same product.

Tiered production: The production of different-quality product lines for different markets.

Time-of-flight mass spectrometry: A method of mass spectrometry in which an ion's mass-to-charge ratio is determined via a time measurement. In this technique, ions are accelerated by an electric field of known strength. This acceleration results in an ion having the same kinetic energy as any other ion that has the same charge. The velocity of the ion depends on the mass-to-charge ratio. The time that it subsequently takes for the particle to reach a detector at a known distance is measured. This time will depend on the mass-to-charge ratio of the particle (heavier particles reach lower speeds). From this time and the known experimental parameters, the mass-to-charge ratio of the ion can be determined.

Track-and-trace: The process of determining past and current locations of a unique item. It gives manufacturers, distributors, and pharmacies a systemic method to detect and control counterfeiting, drug diversions, and mishandling.

Trade dress: Visual characteristics of the appearance of a product or its packaging.

Trademark: Any word, name, symbol, device, or any combination, used or intended to be used to identify and distinguish goods and services of one

seller or provider from those of others, and to indicate the source of the goods and services. Trademarks are registered with the sovereign state and that registration may be used to protect it.

Trademark infringement: A violation of the exclusive rights of a trademark without the authorization of the trademark owner or licensee. Infringement may occur when one party uses a trademark that is identical or confusingly similar to a trademark owned by another party, in relation to products or services that are identical or similar to the products or services that the registration covers.

Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement: Enforced since 1995, the TRIPS agreement is a multilateral agreement on intellectual property. It sets global minimum standards for protecting and enforcing nearly all forms of intellectual property rights, including those for patents.

Transport costs: Costs associated with transporting goods.

Two-dimensional (2D) barcode: A graphical image that stores information with both horizontal and vertical lines. It can store large amounts of data on a variety of goods and products.

Ultraviolet-visible spectroscopy: A technique that examines electronic transitions and allows the wavelength and maximum absorbance of compounds to be determined. This technique is routinely used in analytical chemistry for the quantitative determination of different analytes, such as transition metal ions, highly conjugated organic compounds, and biological macromolecules.

Uniformity of dosage: The degree of uniformity in the amount of the drug substance in dosage units.

United States Adopted Names: Unique nonproprietary names assigned to generic pharmaceuticals marketed in the United States.

United States Adopted Names Council: A five-member council consisting of one member from each sponsoring organization (the American Medical Association, the U.S. Pharmacopeial Convention, and the American Pharmacists Association), one from the U.S. Food and Drug Administration, and another member-at-large. It is responsible for selecting simple, informative, and unique nonproprietary names for drugs by establishing logical nomenclature classifications based on pharmacological and chemical relationships.

Unregistered: A product that lacks market authorization from the national regulatory authority. Though it may be of good quality, an unregistered product is illegal.

U.S. Pharmacopeia Convention: A scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed, and consumed worldwide.

Uterotonic drugs: Medications given to cause a woman's uterus to contract or to increase the frequency and intensity of contractions. The three uterotonic drugs used most frequently are oxytocins, prostaglandins, and ergot alkaloids.

Vibrational spectroscopy: The collective term used to describe two analytical techniques—infrared and Raman spectroscopy. Infrared and Raman spectroscopy are nondestructive, noninvasive tools that provide information about the molecular composition, structure, and interactions within a sample. These techniques measure vibrational energy levels associated with the chemical bonds in a sample. The sample spectrum is unique, like a fingerprint, and vibrational spectroscopy is used for identification, characterization, structure elucidation, reaction monitoring, quality control, and quality assurance.

Visual inspection: The standard first step in any drug quality assessment. It is the inspection of a suspected substandard or falsified pharmaceutical product: looking for differences in color, size, shape, tablet quality, and packaging, and comparing it to an authentic product.

World Health Organization (WHO) essential medicine: Medicines that satisfy the priority health care needs of a population. They are selected according to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness.

World Health Organization (WHO) Model Quality Assurance System for procurement agencies: A system that assists procurement agencies to procure safe, effective pharmaceuticals of suitable quality.

World Health Organization (WHO) prequalification: A service provided to guide United Nations agencies in procuring good-quality products. The prequalification procedures established by the WHO include inspections, dossier reviews, etc., intended to assure the quality, safety, and efficacy of medicinal products.

World Health Organization (WHO) prequalification program: A program managed by the WHO that prequalifies pharmaceutical and other health products that are considered to be acceptable for procurement by the United Nations and specialized agencies, and laboratories for quality control of such products.

X-ray diffraction: A technique used by chemists to examine the physicochemical makeup of unknown solids. Samples of solids are illuminated with X-rays of a fixed wavelength and the intensity of the reflected radiation is recorded. These data are then analyzed for the reflection angle to calculate the inter-atomic spacing, allowing chemists to identify possible matches to the sample.

X-ray fluorescence: The emission of characteristic secondary (or fluorescent) X-rays from a material that has been excited by bombarding the sample with high-energy X-rays or gamma rays. It is widely used for elemental analysis to distinguish between authentic and falsified drugs.

Appendix B

Committee Biographies

Lawrence O. Gostin, J.D. (*Chair*), is professor of law at Georgetown University; professor of public health at the Johns Hopkins University; and the director of the Center for Law & the Public's Health at Johns Hopkins and Georgetown Universities. He is research fellow at the Centre for Socio-Legal Studies at Oxford University. Professor Gostin is a member of the Institute of Medicine (IOM) of the National Academy of Sciences. For the IOM, he serves on the Board on Health Sciences Policy, the Institutional Review Board, and three expert study committees, including the Committee on Assuring the Health of the Public in the 21st Century. He is also an elected lifetime fellow of the Hastings Center. He was appointed by the Secretary of Health and Human Services to serve on the Advisory Council of the Office of AIDS Research at the National Institutes of Health. Professor Gostin also consults for the World Health Organization, UNAIDS (Joint United Nations Programme on HIV/AIDS), and the Council of International Organizations for Medical Sciences. He is the Health Law and Ethics Editor of the *Journal of the American Medical Association*. He is also on the editorial board of scholarly journals.

Professor Gostin has led major law reform initiatives for the U.S. Department of Health and Human Services and a consortium of states. In the wake of September 11, 2001, the Center for Law and the Public's Health drafted the Model Emergency Health Powers Act to combat bioterrorism and other emerging health threats. Professor Gostin was a member of the President's Task Force on National Health Care Reform. His principal areas of work were on the ethical foundations of the new health care system, public health, and privacy. He was formerly executive director of the

American Society of Law, Medicine & Ethics and adjunct professor of law and public health at Harvard University. In the United Kingdom, Professor Gostin was the chief executive of the National Council for Civil Liberties, legal director of the National Association of Mental Health, and faculty member of Oxford University. Professor Gostin received the Rosemary Delbridge Memorial Award from the National Consumer Council (UK) for the person "who has most influenced Parliament and government to act for the welfare of society." He also received the key to Tohoku University in Japan for distinguished contributions to human rights in mental health. Professor Gostin's latest books are both published by the University of California Press and the Milbank Memorial Fund: *Public Health Law: Power, Duty, Restraint* (2000) and *Public Health Law and Ethics: A Reader* (2002).

Daniel Carpenter, Ph.D., A.M., is the Allie S. Freed Professor of Government and director of the Center for American Political Studies in the Faculty of Arts and Sciences at Harvard University. For the 2011-2012 academic year, he was a Walter Channing Cabot Faculty Fellow at Harvard and a visiting researcher at the Institut d'Études Politiques at the Université de Strasbourg in France. He graduated from Georgetown University in 1989 with distinction in government and received his doctorate in political science from the University of Chicago in 1996. He taught previously at Princeton University (1995-1998) and the University of Michigan (1998-2002). He joined the Harvard University faculty in 2002. Professor Carpenter mixes theoretical, historical, statistical, and mathematical analyses to examine the development of political institutions, particularly in the United States. He focuses upon public bureaucracies and government regulation, particularly regulation of health and financial products. His dissertation received the 1998 Harold D. Lasswell Award from the American Political Science Association and as a book, *The Forging of Bureaucratic Autonomy: Reputations, Networks and Policy Innovation in Executive Agencies, 1862-1928*, was awarded the APSA's Gladys Kammerer Prize as well as the Charles Levine Prize of the International Political Science Association. His recently published book on pharmaceutical regulation in the United States is entitled *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* and has received the 2011 Allan Sharlin Memorial Award from the Social Science History Association. Professor Carpenter has held fellowships from the John Simon Guggenheim Foundation, the Radcliffe Institute for Advanced Study, the Center for Advanced Study in the Behavioral Sciences, the Brookings Institute, and the Santa Fe Institute. He has received grants from the National Endowment for the Humanities, the National Science Foundation, the Robert Wood Johnson Foundation, the Alfred P. Sloan Foundation, the Russell Sage Foundation, and the Edmond J. Safra Center for Ethics. Professor Carpenter is the win-

ner of both the 2011 Herbert Simon Award of the Midwest Political Science Association for a scholar "who has made a significant career contribution to the scientific study of bureaucracy," as well as the 2011 David Collier Award of the American Political Science Association for career contributions to qualitative and multi-method research. In addition to his ongoing teaching and scholarship on the political economy of government regulation and health, Professor Carpenter has recently launched a long-term project on petitioning in North American political development, examining comparisons and connections to petitioning histories in Europe and India. He hopes to draw upon the millions of petitions in local, state, and federal archives to create an educational, genealogical, and scholarly resource for citizens, students, and scholars.

Hans Hogerzeil, M.D., Ph.D., FRCP Ed., is a professor of global health at Gronigen University. He qualified as a medical doctor from Leiden University in the Netherlands and received a Ph.D. in public health in 1984. For five years, he was a mission doctor in India and Ghana. In 1985, he joined the World Health Organization (WHO) Action Programme of Essential Drugs, first in the Regional Office for the Eastern Mediterranean in Alexandria, Egypt, and later in the WHO headquarters in Geneva, Switzerland. As a WHO staff member, he has advised more than 40 developing countries on the development of their national medicines policies, essential drugs lists, and essential drugs programs. As secretary of the WHO Expert Committee on the Selection and Use of Essential Medicines, he initiated the recent changes in procedures for updating the Model List of Essential Medicines, which places stronger emphasis on evidence-based selections. He is director of essential medicines and pharmaceutical policies and chair of the Interagency Pharmaceutical Coordination Group. Dr. Hogerzeil is the editor of several WHO books on essential medicines policies, the quality use of medicines, medicines in emergency situations, and essential medicines for reproductive health. He has published more than 50 scientific papers in peer-reviewed journals and teaches every year at international courses all over the world. In 1996 he was invited to become a fellow of the Royal College of Physicians in Edinburgh, Scotland, and in 1998, he received an honorary doctorate of science from the Robert Gordon University in Aberdeen, Scotland.

Ann Marie Kimball, M.D., M.P.H., is a senior program officer in epidemilogy and surveillance at the Bill & Melinda Gates Foundation. she was previously a professor and director of the master's in public health program at the University of Washington School of Public Health and Community Medicine. She is also adjunct professor in medicine with the University of Washington School of Medicine. Her research interests are in emerging

infections and global epidemic, prevention, surveillance, investigation, and control of infectious diseases. She has worked extensively in the areas of trade policy and disease control and telecommunications and disease surveillance and alert systems. Formerly, Dr. Kimball served as Regional Advisor for HIV/AIDS with the Pan American Health Organization. She has also served as director of the Washington State HIV/AIDS/STD Program with the state Department of Health and as chair of the National Alliance of State and Territorial AIDS Directors in the United States. Dr. Kimball has served on numerous editorial and scientific and technical committees. She serves on the editorial board of the *Control of Communicable Diseases Manual* (APHA, 2000) and as a member of the Institute of Medicine committee to review the Global Emerging Infections Surveillance program. She is a fellow of the American College of Preventive Medicine. She is chair of the University of Washington Hogness Symposium.

Thomas P. Layloff, Ph.D., M.S., is a principal program associate at Management Sciences for Health (MSH) who works on pharmaceutical product and laboratory quality issues with both the Rational Pharmaceutical Management Plus and Strategies for Enhancing Access to Medicines programs. He has over 25 years' experience directing U.S. Food and Drug Administraiton pharmaceutical control laboratory operations and more than 10 years of service as an elected expert on the Committee of Revision of the U.S. Pharmacopeia (USP), which included 5 years on the Reference Standards Committee, 5 years as chair of the General Chapters Committee, and 2 years as chair of the Division of Standards Development Executive Committee. Prior to joining MSH, he served at USP as vice president and director of the Pharmaceutical Standards Division. He is a past president and elected fellow of AOAC International, a nonprofit scientific association that publishes chemical analysis methods. He is also a charter member and elected fellow of the American Association of Pharmaceutical Scientists. Dr. Layloff received a B.A. in psychology and chemistry and M.S. in organic chemistry from Washington University in St. Louis, Missouri. He received a Ph.D. in analytical chemistry with a minor in mathematics from the University of Kansas in Lawrence.

Patrick Lukulay, Ph.D., is currently the director of the United States Agency for International Development–funded program Promoting the Quality of Medicines, implemented by U.S. Pharmacopeia. He oversees the work of about 20 staff to provide technical assistance to developing countries to strengthen quality assurance and quality systems for pharmaceuticals. Dr. Lukulay has a Ph.D. in analytical chemistry from Michigan State University. He worked in the pharmaceutical industry for Wyeth and Pfizer for a combined 12 years as senior principal scientist. He is the author of several

articles in separation science and spectroscopy and is a frequent speaker and national and international conferences.

Margareth Ndomondo-Sigonda, M.Sc., M.B.A., served as director general of the Tanzania Food and Drugs Authority for 7 years and registrar of the Tanzanian Pharmacy Board for 5 years before that. Ms. Ndomondo-Sigonda has been involved in medicines regulation harmonization initiatives in the Southern Africa Development Community and East African Community. She has consulted for the World Health Organization on assessment of medicines regulatory systems in Carribean Community member states, the Dominican Republic, Egypt, Kenya, Sudan, and Zambia. She has also been a consultant for the assessment of medicines regulatory systems in Egypt, Kenya, Sudan, and Zambia. She now works as a pharmaceutical coordinator for the African Union New Partnership for Africa's Development. Ms. Ndomondo-Sigonda is responsible for coordinating the pharmaceutical development programs, including the African Medicines Regulatory Harmonization initiative. She has a master's degree in pharmaceutical services from the University of Bradford in the United Kingdom, an M.B.A. from Maastricht School of Management in the Netherlands, and a bachelor's degree in pharmacy from the University of Dar es Salam.

Arti K. Rai, J.D., is the Elvin R. Latty Professor of Law at Duke University Law School and a member of the Duke Institute for Genome Science and Policy. She is an authority in patent law, administrative law, and innovation policy. Ms. Rai has also taught at Harvard, Yale, the University of Pennsylvania, and the University of San Diego law schools. Ms. Rai's academic research on innovation policy in areas such as synthetic biology, green technology, drug development, and software has been funded by the National Institutes of Health (NIH), the Kauffman Foundation, and Chatham House. She has published widely in both peer-reviewed journals and law reviews, including *Nature Biotechnology*, *PLoS Biology*, *PLoS Medicine*, the *Annals of Internal Medicine*, and the Columbia, Georgetown, and Northwestern law reviews. She is the editor of *Intellectual Property Law and Biotechnology: Critical Concepts* (Edward Elgar, 2011) and has also co-authored a casebook on law and the mental health system.

From 2009 to 2010, Ms. Rai took a leave of absence from Duke Law School to serve as the administrator of the Office of External Affairs at the U.S. Patent and Trademark Office. Prior to that, she served on President-Elect Obama's transition team reviewing the Patent and Trademark Office and as an expert advisor to the Department of Commerce's Office of General Counsel. Prior to entering academia, Ms. Rai clerked for the Honorable Marilyn Hall Patel of the U.S. District Court for the Northern District of California; was a litigation associate at Jenner & Block (doing patent

litigation as well as other litigation); and was a litigator at the Federal Programs Branch of the U.S. Department of Justice's Civil Division. Ms. Rai has served as a peer reviewer for *Science*, *Research Policy*, the *Journal of Legal Studies*, various National Academy of Sciences reports on intellectual property, and various NIH study sections. She has also testified before Congress on innovation policy issues and regularly advises federal agencies on policy issues (including intellectual property policy issues) raised by the research that they fund. Recently, her work has focused on advising the Defense Advanced Research Projects Agency. Ms. Rai is currently the chair of the Intellectual Property Committee of the Administrative Law Section of the American Bar Association. She is also a fellow of the American Bar Foundation. In 2011, Ms. Rai won the World Technology Network Award for Law.

Ms. Rai graduated from Harvard College, magna cum laude, with a B.A. in biochemistry and history (history and science), attended Harvard Medical School for the 1987-1988 academic year, and received her J.D., cum laude, from Harvard Law School in 1991.

Marco Antonio Stephano, M.S., Ph.D., is a veterinarian and pharmaceutical biochemist at the University of São Paulo. He worked for 14 years at the Butantan Institute as a researcher in serums and vaccines in applied immunology and served as director of quality assurance there for 4 years. Currently, Dr. Stephano is a professor at the Pharmaceutical Sciences School in quality assurance and biotechnology. He is a member of the Brazilian Pharmacopoeia in the area of biological products. He holds a master's degree in pharmacology from Campinas State University and a doctorate in pharmaceutical biochemistry from University of São Paulo.

John Theriault, M.B.A., has had senior leadership roles with the Federal Bureau of Investigation, Pfizer, and Apple. Today, he is recognized internationally as an expert on the subject of product counterfeiting and the development of effective programs to combat its far-ranging impact on society. Mr. Theriault served as a special agent of the Federal Bureau of Investigation (FBI) for more than 25 years, rising to the Bureau's Senior Executive Service. For 7 years he was diplomatically accredited as the legal attaché at various U.S. embassies and was responsible for managing all of the FBI's law enforcement, counterintelligence, and counterterrorism relationships with senior government officials of the host countries. In 1996 he joined Pfizer as vice president and chief security officer. In response to widespread counterfeiting of their medicines, he created, staffed and led the company's global anti-counterfeiting program, which became a model for the industry. He has testified before the U.S. Senate Special Committee on Aging, the U.S. House of Representatives Committee on Energy and Commerce, and

the U.S. Surgeon General's Drug Importation Task Force. He has briefed the U.S. Secretary of Commerce and other senior government officials on the dangers of counterfeit medicines, and he has appeared on a number of broadcasts including *60 Minutes*, *Larry King Live*, *CNN Late Edition*, *BBC Radio*, and others. In 2007 Mr. Theriault was recruited by Apple to create a global security organization with a strong focus on combating their growing counterfeiting problem. In November 2011 he retired from Apple to return to the East Coast and pursue other interests. Mr. Theriault earned a B.A. from the University of Memphis and an M.B.A. degree from Emory University.

Mary E. Wilson, M.D., is an associate professor of Global Health and Population at the Harvard School of Public Health. Her academic interests include the ecology of infections and emergence of microbial threats, travel medicine, tuberculosis, and vaccines. Her undergraduate degree in French, English, and philosophy was awarded by Indiana University; she received her M.D. from the University of Wisconsin and completed an internal medicine residency and infectious disease fellowship at the Beth Israel Hospital in Boston (now Beth Israel–Deaconess Medical Center). Dr. Wilson was chief of infectious diseases at Mount Auburn Hospital, a Harvard-affiliated community teaching hospital in Cambridge, Massachusetts, for more than 20 years. She is a fellow in the Infectious Diseases Society of America and the American College of Physicians. Dr. Wilson has served on the Advisory Committee for Immunization Practices of the U.S. Centers for Disease Control and Prevention, the Academic Advisory Committee for the National Institute of Public Health in Mexico, and on four committees for the Institute of Medicine of the National Academies, including the Committee on Emerging Microbial Threats to Health in the 21st Century. She has worked in Haiti at the Albert Schweitzer Hospital and leads the Harvard–Brazil Collaborative Course on Infectious Diseases, which is taught in Brazil. In 1996 she was a resident scholar at the Bellagio Study Center, Italy, and in 2002 she was a fellow at the Center for Advanced Study in the Behavioral Sciences in Stanford, California. Dr. Wilson was member of the Pew National Commission on Industrial Farm Animal Production whose report, *Putting Meat on the Table: Industrial Farm Animal Production in America*, was released in the spring of 2008. A former GeoSentinel site director, she now serves as a special advisor to the global GeoSentinel Surveillance Network. She has lectured and published widely, serves on several editorial boards, and is an associate editor for *Journal Watch Infectious Diseases*. She is the author of *A World Guide to Infections: Diseases, Distribution, Diagnosis*; senior editor, with Richard Levins and Andrew Spielman, of *Disease in Evolution: Global Changes and Emergence of Infectious Diseases*; and editor of the volume *New and Emerging Infectious Diseases*, published

in 2008. She joined the Board of Trustees for the International Centre for Diarrheal Disease Research, Bangladesh and is a member of the Board of Scientific Counselors for the Centers for Disease Control and Prevention, the FXB-USA board, and the Alliance for Prudent Use of Antibiotics Board of Directors.

Prashant Yadav, Ph.D., M.B.A., is a senior research fellow and director of the Healthcare Research Initiative at the William Davidson Institute at the University of Michigan. Previously he was a professor in Supply Chain Management at the Massachusetts Institute of Technology (MIT)-Zaragoza International Logistics Program and a research affiliate at the MIT Center for Transportation and Logistics. Dr. Yadav's research explores the functioning of pharmaceutical supply chains using a combination of empirical, analytical, and qualitative approaches. His more recent work involves supply chains for medicines in sub-Saharan Africa and other poor countries. In this work he collaborates closely with leading policy organizations and philanthropic foundations. Dr. Yadav serves as a consultant and adviser in the area of pharmaceutical supply chains to the World Bank, World Health Organization, UK Department for International Development, Roll Back Malaria Partnership, the Bill & Melinda Gates Foundation, the Medicines for Malaria Venture, and many other global health organizations. He is the author of many scientific publications and his work has been featured in prominent print and broadcast media. Dr. Yadav obtained his bachelor's degree in engineering from the Indian Institute of Technology, his M.B.A. from the FORE School of Management, and his Ph.D. from the University of Alabama. Before academia, he worked for many years in the area of pharmaceutical strategy, analytics, and supply chain consulting.

Appendix C

Meeting Agendas

March 12-13, 2012
Meeting 1—Agenda
Washington, DC

DAY ONE: MONDAY, MARCH 12, 2012

Session 1 – Closed
IOM Committee Process and Charge to Committee
Room 204

Objective: To review the National Academies' study process that includes a bias and conflict of interest discussion; to discuss the role of the committee in addressing the statement of task; and to ensure the committee understands its statement of task.

Session 2 – Open
Questions on Statement of Task
Room 100

11:10-11:30 Project Timeline and Statement of Task
Sponsor Representative Introductions
Larry Gostin, Committee Chair

11:30-11:45 The Charge to the Committee
Jennifer Devine, Deputy Director, Global Regulatory Operations & Policy, FDA
Kate Bond, Associate Director for Technical Cooperation and Capacity Building, FDA

11:45-12:15 Questions

12:15-1:15 Lunch

Session 3 – Open
Technologies for Detecting Unsafe Drugs
Room 100

1:15-1:25 Welcome and Introductions
Larry Gostin, Committee Chair

1:25-1:45 The Strengths and Weaknesses of the Detection Technologies Currently Available
Mark Witkowski, Supervisory Chemist, Trace Examination Section, Forensic Chemistry Center, FDA

1:50-2:10 Importance of Reliable Detection Technologies in the Field
Ashifi Gogo, Chief Executive, Sproxil

2:15-2:30 Break

2:30-2:50 Using Analytic Detection Technologies in Singapore
Lim Chin Chin, Forensic Laboratory Director and Forensic Scientist, Singapore Health Science Authority

2:55-3:15 Using Analytic Detection Technologies in Peru
Percy Alberto Ocampo Rujel, former Executive Director, Directorate of Control and Health Surveillance, Peru

3:20-3:40 Case Study on Merck's Use of Detection Technologies
Anthony Zook, Director of Anti-Counterfeiting, Merck

3:45-4:30 Panel Discussion, The Future of Reliable Detection Technologies in the Field
Patrick Lukulay, Moderator

Session 4 – Closed
Committee Planning

DAY TWO: TUESDAY, MARCH 13, 2012
ROOM 100

Session 5 – Open
Framing and Defining the Problem

8:15-8:30	Opening Remarks **Mary Lou Valdez,** Associate Commissioner, Office of International Programs, FDA
8:45-9:45	Varying Interpretations of the Terms Counterfeit, Falsified, and Substandard **Howard Zucker,** Senior Advisor, Massachusetts General Hospital **Rohit Malpani,** Senior Advisor for Campaigns, Oxfam America **Roger Bate,** Legatum Fellow in Global Prosperity, American Enterprise Institute **David R. Gaugh,** Vice-President for Regulatory Science, Generic Pharmaceutical Association
9:45-10:15	Panel Discussion on Terminology and the Problem of Fake Drugs **Bryan Liang,** Moderator
10:15-10:30	Break
10:30-11:45	Economic and Trade Interests in Counterfeit, Falsified, and Substandard Drugs **Nicholas Cappuccino,** Chief Executive, Pharmaceutical Intellectual Resource Services, LLC **John Clark,** Chief Security Officer and Vice President of Global Security, Pfizer **Jamie Love,** Director, Knowledge Ecology International
11:45-12:15	Panel Discussion on Health, Economic, and Trade Dimensions of the Problem **Prashant Yadav,** Moderator
12:15-1:15	Lunch

Session 6 – Open
National and International Collaboration

1:15-2:15 Enforcement in Pharmaceutical Fraud
- **Susanne Keitel,** Director, European Directorate for Quality of Medicines and Healthcare, Council of Europe
- **Aline Plançon,** Manager, Interpol Medical Products Counterfeiting and Pharmaceutical Crime Unit (by video conference)
- **Sebastian Mollo,** Intelligence Director, Pharmaceutical Security Institute
- **Sameer Barde,** Federation Indian Chambers of Commerce and Industry
- **Daniel Carpenter,** Moderator

2:25-3:30 U.S. Government Work Against Pharmaceutical Fraud
- **Catherine Hill-Herndon,** Director, Office of International Health and Biodefense, U.S. Department of State
- **Linda Marks,** Attorney, U.S. Department of Justice
- **Jeffery Gren,** Director, Office of Health and Consumer Goods, U.S. Department of Commerce
- **Ilisa Bernstein,** Director, Office of Compliance, Center for Drug Evaluation Research, FDA
- **Margareth Ndomondo-Sigonda,** Moderator

3:30-3:45 Break

Session 7 – Open
Scope of Work on the Problem

3:45-4:30 Investigating Trends and Analyzing Policy in Pharmaceutical Fraud
- **Laurie Garrett,** Senior Fellow for Global Health, Council on Foreign Relations
- **Alan Coukell,** Director Medical Programs, Pew Health Group
- **Judit Rius,** U.S. Manager of the Campaign for Access to Essential Medicines, Doctors Without Borders
- **Ann Marie Kimball,** Moderator

4:30-5:00 Closing Remarks
Larry Gostin, Committee Chair

5:00 Adjourn

May 9-10, 2012
Meeting 2—Agenda
Washington, DC

DAY ONE: WEDNESDAY, MAY 9, 2012
ROOM 110

All sessions were closed. Committee members discussed the report and potential conclusions and recommendations.

DAY TWO: THURSDAY, MAY 10, 2012
ROOM 206

Session 5 – Open
FDA Data on Fake Drugs

10:30-11:30 The FDA's estimates of the scope of the problem
Jen Devine, Regulatory Counsel, CDER Office of Compliance

11:30-12:00 Questions

June 26-July 4, 2012
Travel Meeting—Agenda
Geneva, London, New Delhi, Hyderabad

DAY ONE: TUESDAY, JUNE 26, 2012
GENEVA, SWITZERLAND

3:15-3:30 Travel to Global Fund

3:30-5:00 Meeting at Global Fund
Joelle Daviaud, Quality Assurance Specialist and Grant Management Support, the Global Fund to Fight AIDS, Tuberculosis, and Malaria

Mariatou Tala Jallow, Manager, Procurement Support Service, the Global Fund to Fight AIDS, Tuberculosis, and Malaria

DAY TWO: WEDNESDAY, JUNE 27, 2012
GENEVA, SWITZERLAND

9:15-10:00	Working breakfast for committee members and staff at Movenpick Hotel
10:30-11:30	**Amir Attaran,** Associate Professor, Faculties of Law and Medicine, University of Ottawa
12:30-1:45	Lunch
1:45-2:00	Travel to South Centre
2:00-3:30	Meeting at South Centre **German Velasquez,** Senior Advisor of Health and Development, South Centre **Nirmalya Syam,** Program Officer, Innovation and Access to Knowledge Program, South Centre
3:30-4:00	Travel to NGO Forum for Health
4:00-5:00	Meeting with NGO Forum for Health **Alan Leather,** President, NGO Forum for Health

DAY THREE: THURSDAY, JUNE 28, 2012
GENEVA, SWITZERLAND

8:30-9:15	Working breakfast for committee members and staff at Movenpick Hotel
9:15-9:30	Travel to WHO
9:30-11:00	Meeting at WHO with Interpol **Aline Plançon,** Enforcement Officer, Interpol **Naill Sargent,** Criminal Intelligence Analyst, Interpol
11:45-12:00	Travel to Third World Network

12:00-1:30	Meeting at Third World Network **Sangeeta Shashikant,** Legal Advisor, Third World Network
1:30-2:15	Lunch
2:15-2:30	Travel to WHO
2:30-5:00	Meeting at WHO **Kees de Joncheere,** Regional Adviser, Health Technology and Pharmaceuticals, WHO **Sabine Kopp,** Manager, Medicines Quality Assurance Program, WHO **Michele Forzley,** Professor, Widener School of Law and Georgetown School of Law

DAY FOUR: FRIDAY, JUNE 29, 2012
LONDON, ENGLAND

8:30-9:45	Working breakfast for committee members and staff at Thistle Grosvenor Hotel
9:45	Travel to EMA
10:30-12:00	Meeting at EMA **Emer Cooke,** Acting Head, International and European Cooperation, EMA
12:00-1:30	Lunch
1:30-2:00	Travel to Chatham House
2:00-5:00	Meeting at Chatham House **Charles Clift,** Senior Research Consultant, Centre on Global Health Security, Chatham House **Paul Newton,** Director, Wellcome Trust-Mahosot Hospital-Oxford University Tropical Medicine Research Collaboration **Harparkash Kaur,** Professor, London School of Hygiene and Tropical Medicine **Sharon Peacock,** Professor, University of Cambridge **Simeon Wilson,** Director, Global Security, AstraZeneca

Paul Ellis, Director, External Advocacy, GlaxoSmithKline
Mohga Kamal-Yanni, Senior Health and HIV Policy Adviser, Acting Team Lead Development Finance and Public Service, Oxfam
Philippa Saunders, Consultant
Wendy Greenall, Counterfeit Medicines Laboratory Manager, Pfizer
Greg Perry, Director General, European Generic Medicines Association
Francis Roodt, Intellectual Property Office
Lynda Scammell, Senior Policy Manager and Relationship Manager, Enforcement Group, Medicines and Healthcare Products Regulatory Agency

DAY FIVE: MONDAY, JULY 2, 2012
NEW DELHI, INDIA

7:00-7:45	Working breakfast for committee members and staff at Crowne Plaza Hotel
7:45	Travel to PATH
8:30-10:00	Meeting at PATH **Raj Shankar Ghosh,** Technical Director, PATH **Sonali Kochhar,** Medical Director, PATH **Pritu Dhalaria,** Director, Immunization Projects, PATH **Satish Kaipilyawar,** Project Director, TB Program, PATH
10:00-11:00	Travel to Ministry of Health and Family Welfare
11:00-12:30	Meeting at Ministry of Health and Family Welfare **L.C. Goyal,** Additional Secretary and Director General, Central Government Scheme, Ministry of Health and Family Welfare **Arun Panda,** Joint Secretary, Ministry of Health and Family Welfare
12:30-1:30	Lunch

1:30-2:00	Travel to Pharmacy Council of India
2:00-3:00	Meeting at Pharmacy Council of India **Archana Mudgal,** Pharmacy Council of India
3:00-3:30	Travel to U.S. Embassy
3:30-5:00	Meeting at U.S. FDA **Bruce Ross,** Director, India Office, FDA **Regina Brown,** Assistant Director of Medicines, FDA **Albinus D'Sa,** Deputy Director, India Office, FDA **Nirupa Sen,** Food and Medical Product Safety Coordinator, FDA

DAY SIX: TUESDAY, JULY 3, 2012
NEW DELHI, INDIA

8:15-9:00	Working breakfast for committee members and staff at Crowne Plaza Hotel
9:00-10:30	Meeting with Serum Institute **Sunil Bahl,** Director, Business Development, Serum Institute of India **Pramod Kumar,** Senior Manager, Serum Institute of India
10:30-12:00	Meeting with Indian Pharmaceutical Alliance **Dilip Shah,** Secretary General, Indian Pharmaceutical Alliance
12:00-1:00	Lunch
1:00-1:30	Travel to Delhi Society for Promotion of Rational Use of Drugs
1:30-3:00	Meeting at Delhi Society for Promotion of Rational Use of Drugs **Ranjit Chaudhury,** Director, India-WHO Program in Rational Use of Drugs **Usha Gupta,** Executive Vice President, Delhi Society for Promotion of Rational Use of Drugs

3:00-3:30	Travel to Partnership for Safe Medicines India
3:30-5:00	Meeting at Partnership for Safe Medicines India **Bejon Misra,** Founder, Partnership for Safe Medicines India
5:00	Travel to airport
7:30	Flight to Hyderabad

DAY SEVEN: WEDNESDAY, JULY 4, 2012
HYDERABAD, INDIA

7:30-8:15	Working breakfast for committee members and staff at Westin Hotel
8:15	Travel to USP-India
9:00-11:00	Overview of USP-India's activities and laboratory tour **Koduru Surendra Nath,** Senior Vice President, USP-India
11:00-12:00	Travel to Gland Pharma Limited
12:00-2:00	Lunch Meeting at Gland Pharma Limited **Subhash Gouda,** Deputy Manager, International Business, Gland Pharma Limited **Srinivas Sadu,** Chief Operating Officer, Gland Pharma Limited
2:00-3:00	Travel to Pharmexcil-India
3:00-4:30	Meeting with industry and industry associations **P.V. Appaji,** Director General, Pharmexcil India **Meghana Inamdar,** General Counsel and Managing Consultant, Sidvim Lifesciences

August 27-29, 2012
Travel Meeting—Agenda
São Paulo and Brazília, Brazil

DAY 1: MONDAY, AUGUST 27, 2012
SÃO PAULO, BRAZIL

8:15-9:00	Working breakfast for committee members and staff at hotel
9:00	Travel to University of São Paulo
9:30-10:45	**Débora Germano,** Associate Director, Regulatory Affairs, Pfizer **Claudia Lima,** Latin America Packaging Operational Services Manager, Pfizer **Rodrigo Lozano,** Director, Distribution Center Operations, Pfizer **Erica M. Varise,** Compliance Manager, Logistics Operations, Pfizer **Alberto C. Santos,** Corporate Security Manager, Pfizer **Luciano Rosado,** Quality Assurance Manager, Libbs Farmaceutica Group
10:45-11:30	**Nicolina Romano-Lieber,** Associate Professor, Department of Public Health Practices, School of Public Health, University of São Paulo
11:30-1:00	Lunch
1:00-1:45	**Douglas Duarte,** Technical Regulatory Manager, National Pharmaceutical Industries Association
1:45	Adjourn

DAY TWO: TUESDAY, AUGUST 28, 2012
SÃO PAULO, BRAZIL

8:15-9:00	Working breakfast for committee members and staff at hotel

9:00	Travel to University of São Paulo
9:30-10:45	**Fernando Nogueira,** Professor, Federal University of Minas Gerais **Claudio Cabral,** Director of Quality, Cristália Laboratory **Regina Zamith,** Director, Global Brand Protection Latin America, Johnson & Johnson
10:45-11:00	Break
11:00-12:15	**Terezinha Pinto,** Professor, School of Pharmaceutical Sciences, University of São Paulo **Filipe Soares Quirino da Silva,** Director, Department of Chemistry, National Institute for Health Quality, Fiocruz **Ediná Costa,** Associate Professor, Institute of Collective Health, Federal University of Bahia
12:15-1:15	Lunch
1:15-2:30	**Elize Massard,** Postdoctoral Research Fellow, Center for Metropolitan Studies **Aluisio Segurado,** Professor, School of Medicine, Department of Infectious and Parasitic Diseases, University of São Paulo
2:30-3:00	Break
3:00-4:00	**Frederico Benite,** Principal Business Development Officer, International Finance Corporation/ World Bank Group **Paulo Teixeira,** Second Vice-President, National Federation of Pharmacists
4:00	Adjourn

DAY THREE: WEDNESDAY, AUGUST 29, 2012
BRASÍLIA, BRAZIL

7:15-8:00	Working breakfast for committee members and staff at hotel
8:00	Travel to Anvisa
9:00-10:00	Meeting with Anvisa's President **Dirceu Barbano,** President, Anvisa
10:00-10:30	Travel to PAHO
10:30-11:45	Meeting at PAHO **Christophe Rerat,** International Officer and Coordinator, Medicines Unit, Technology and Research, PAHO **Flavia Poppe,** Health Economist, Medicines Unit, Technology and Research, PAHO
11:45-12:15	Travel to Hotel Manhattan
12:15-2:00	Meeting at Hotel Manhattan **Paola Manchesini,** Technical Consultant, Malaria National Control Program, Brazilian Ministry of Health **Marcia Almeida,** Technical Consultant, Drug Management Department, National Malaria Control Program, Brazilian Ministry of Health **Mayira Milano,** International Consultant, Technical Unit for Non-Communicable and Communicable Diseases, PAHO
2:00-3:00	Lunch
3:00-3:30	Travel to Anvisa
3:30-5:00	Meeting with Anvisa's International Office **Tiago Lanius Rauber,** Director, Inspection and Control of Medicines and Products, Anvisa **Patricia Oliveira Pereira,** Deputy Director, International Health Regulations Unit, Division of International Affairs, Anvisa **Leandro Teixeira de Morais,** Specialist, International Health and Health Surveillance, Anvisa