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United States Pharmacopeia

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Drug Quality and Information Program

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# A Review of Drug Quality in Asia with Focus on Anti-Infectives

February 2004

USP
U.S. PHARMACOPEIA
*The Standard of Quality*[SM]

# ACKNOWLEDGEMENTS

The United States Pharmacopeia (USP) is a private, nonprofit volunteer-driven organization. It has been a trusted and recognized pharmaceutical standards-setting authority in the U.S. since 1820, whose standards are used in at least 35 countries. Since 1975, USP has been developing authoritative, unbiased information that has gone through evidence-based review process involving the USP volunteer experts.

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# TABLE OF CONTENTS

# EXECUTIVE SUMMARY

Drug quality is a source of great concern worldwide, particularly in many developing countries. Recent reports indicate that the availability of substandard and counterfeit (fake) drugs has reached a disturbing proportion in resource-poor settings, such as in most Asian countries. Use of poor quality drugs produces serious health implications and wastes resources.

This paper reviews the drug quality, with focus on anti-infective drugs, in selected developing countries in Asia because of the increasing resistance to these drugs resulting in increased morbidity/mortality.

Substandard drugs are genuine products that do not conform to the pharmacopeial standards set for them. Counterfeit drugs, according to the World Health Organization (WHO) are "products that are deliberately and fraudulently mislabeled with respect to identity and/or source."

Eleven Asian countries ─ Bangladesh, Cambodia, China, India, Indonesia, Lao People's Democratic Republic (Laos), Myanmar (Burma), Pakistan, Philippines, Thailand, and Vietnam ─ were selected for this review, mainly because drug quality information (studies and reports) on these countries were readily available.

Among the pharmaceutical products surveyed and reported, a good number of anti-infectives, such as antimicrobials, antiparasitics, antimalarials, anti-tuberculosis, and antivirals, were included. The drugs reported were amoxicillin, ampicillin, ampicillin/cloxacillin, artesunate, ceftazidine, cephalexin, chloramphenicol, chloroquine, ciprofloxacin, cotrimoxazole, diphtheria-pertussis-tetanus vaccine, doxycycline, erythromycin, griseofulvin, hepatitis B vaccine, isoniazid, mebendazole, mefloquine, metronidazole, norfloxacin, ofloxacin, penicillin, praziquantel, quinine, rifampicin, tetracycline, and zidovudine. The reported percentage of substandard/counterfeit drugs ranges from 2% to greater than 60%.

Based on the information presented in the country studies/reports, gaps and weaknesses were identified to include: a) a weak national drug regulatory authority and weak enforcement of drug laws; b) little or no GMP compliance by manufacturers; c) limited laboratory capacity in terms of qualified staff and equipment; d) lack of competent drug inspectors; and e) lack of inexpensive, quality assured drugs.

Most of these countries have already stepped up their efforts to combat the widespread availability of poor quality drugs by raising awareness, conducting additional inspections on companies suspected of producing counterfeit drugs, strengthening drug laws and imposing stiffer penalties for offenders, increasing post-marketing surveillance, restructuring the drug regulatory system, or adopting a social marketing program to improve the availability of quality-assured drugs.

This review concludes that the availability of poor quality drugs, especially anti-infectives, is widespread in Asia and the problem needs to be addressed. Use of these drugs endangers lives, wastes scarce resources, and contributes to drug resistance. Efforts to combat this problem should be undertaken on all levels. At the national level, recommendations include: Strengthening the drug quality assurance system; asserting strong political will and securing commitment from the government to improve drug quality by enacting comprehensive

drug regulations; strengthening or establishing adequately resourced drug regulatory authorities; increasing the number of adequately trained drug inspectors; establishing a drug quality control laboratory with adequate equipment and trained personnel; strengthening law enforcement; enhancing cooperation among stakeholders; increasing the availability of inexpensive, quality assured drugs; reducing or eliminating corruption; and raising awareness of the problem of counterfeit or substandard drugs among health care professionals and the consumers.

At the international level, there should be cooperation between the governments and drug regulatory authorities of drug exporting countries and between governments and international organizations, such as the WHO. International surveillance should be coordinated and information needs to be shared not only with government drug regulatory authorities, but also with customs, police organizations, pharmaceutical companies, nongovernmental organizations, health care providers, and consumers through appropriate means of communication. Pharmaceutical manufacturers should demonstrate vigilance toward setting up appropriate security measures to detect and prevent the counterfeiting of their products. Wholesalers and traders should be cautious in the procurement of active pharmaceutical ingredients and finished products, particularly when introducing products into the distribution chain. Country-specific recommendations also have been described in this review.

The USP panel and ad hoc reviewers agreed on the recommendations set forth in this document. In addition, they recommended the following measures: An executive summary of this review should be developed and disseminated to the media worldwide, to include a list of countries that are not in compliance with world standards; the dangers of adulterated drugs should be explained as well as the reason why regulations and law enforcement are necessary; international pressure should be exerted on target countries to "clean up" and enforce their quality control programs; the WHO, European Union, and U.S. State Department should issue "travelers advisories" about the dangers of taking adulterated drugs in listed countries (countries that comply with international standards can be taken off the list once compliance is assured; such strategy was found to be highly effective in controlling the severe acute respiratory syndrome (SARS) epidemic); the international community should work together to develop a plan for collecting additional, high quality data on drug quality through standardized and strategic sampling to fill gaps (e.g., antiretrovirals for HIV) or monitor new initiatives (e.g., Global Fund to Fight AIDS, Tuberculosis and Malaria) that will increase the availability of anti-infective drugs; and national/regional counterparts should work together to set up more routine monitoring of drug quality.

# I.    INTRODUCTION

Pharmaceutical products play an important role in improving the health and promoting the well-being of every individual. These medicines aid in the prevention and treatment of diseases, disorders, or conditions. These agents can provide relief of symptoms and favorably modify the course of diseases. The three criteria considered the cornerstone for these products ─ quality, effectiveness, and safety — should be demonstrated and verified prior to their rational use. (1)

The issue of drug quality is in the interest of the following parties because each has a stake in them: a) consumers – cure and cost; b) prescribers – patient trust, future visits, future income; c) pharmaceutical companies – reputation, trust in their products, future profits; and d) governments – protection of public health and prevention of increased public expenditure for drugs. (2)

Drug quality is a source of great concern worldwide, particularly in many developing countries. Recent reports (3, 4) indicate that the availability of substandard and counterfeit (fake) drugs has reached a disturbing proportion in resource-poor settings, as in most Asian countries. The rising cost of drugs generally creates a corresponding increase in incentive to produce counterfeit drugs because of profit margin. (2) Use of poor quality drugs has serious health implications (see section on *Consequences of using poor quality drugs*) and wastes resources.

This paper reviews the drug quality, with focus on anti-infective drugs, in selected developing countries in Asia due to the increasing resistance to these drugs which results in increased morbidity and mortality. This desk review may help develop mechanisms to routinely monitor drug quality and apply interventions in the region. Current treatment regimens need protection from the emergence and spread of drug resistance, which is probably exacerbated by use of substandard medicines.

**Causes of poor drug quality**

Poor drug quality can be the result of poor manufacturing practices, counterfeiting, or inappropriate drug storage in excessive heat, moisture, or light. (5, 6, 7, 8, 9)

*Substandard drugs*

Substandard drugs are genuine products that do not conform to the pharmacopeial standards set for them. (3) The quality standards and specifications usually are set by the manufacturer and then published in official pharmacopeias.*

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* A *pharmacopeia* is a book consisting of a list of medicinal substances (drugs) with descriptions, specifications, tests, and acceptance criteria, specified by some recognized authority. In most countries, the recognized authority that issues the books of standards is the government. In the United States (U.S.), however, the book is published by the U. S. Pharmacopeia, a private non-profit organization. Such books of standards include the *British Pharmacopeia* (BP), *European Pharmacopeia* (EP), *International Pharmacopeia* (IP), *Japanese Pharmacopeia* (JP), *United States Pharmacopeia* (USP), etc. (10) USP contains both drug substances and dosage forms. EP generally has only drug substances, but contains a very small number of dosage forms for recombinant-deoxyribonucleic acid (DNA) products. BP has both drug substances and dosage forms. JP has both drug substances and dosage forms (but fewer dosage forms than in USP). IP has both drug substances and dosage forms, but has few monographs. (11)

Substandard products are often made without complying with good manufacturing practices (GMP)[**] due to a lack of expertise or manufacturing infrastructure. (12)

The World Health Organization (WHO) defines a substandard product as "a product with genuine packaging with incorrect quantity of ingredient (not deliberate)." (13) In a recent USP malaria sentinel surveillance assessment report, a substandard product is defined as "a legally branded or generic product, but one that does not meet international standards for quality, purity, strength, or packaging.

A substandard product could:

- Contain no active ingredient, but harmless inactives;

- Contain harmful or poisonous substances;

- Be unregistered in the country where it is sold, or have been manufactured clandestinely, or smuggled into the country and thus be on sale illegally;

- Have been registered inadvisably by a weak drug regulatory agency (e.g., those national authorities lacking in skill and/or resources to properly evaluate product dossiers); or

- Have passed its expiration date." (14)

*Counterfeit drugs*

The legal definition of counterfeit drug varies from country to country. The WHO defines a counterfeit pharmaceutical product as "a product that is deliberately and fraudulently mislabeled with respect to identity and/or source. Based on this definition, counterfeit products may include products with correct ingredients, wrong ingredients, without active ingredients, with incorrect quantity of active ingredient or with fake packaging." (15) The most commonly counterfeited drugs in developing countries are the anti-infectives and anti-parasitics. (13)

Section 201 [321] (g) (2) of the U.S. Federal Food, Drug, and Cosmetic Act defines a counterfeit drug as "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." (16).

At the Global Forum on Pharmaceutical Anti-Counterfeiting held in Geneva in 2002, Benjamin England of the U.S. Food and Drugs Administration (FDA) reported that "counterfeit drugs are, by definition, outside the regulatory regime the U.S. Congress created and the U.S. FDA enforces to ensure the highest quality, safety, and efficacy of drugs.

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[**] *GMP* refers to "regulations, which have the force of law, which require that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood take proactive steps to ensure that their products are safe, pure, and effective. GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors. This in turn, protects the consumer from purchasing a product that is not effective or even dangerous. GMP regulations address issues including record keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling." (17)

Counterfeit drugs may:

- Be subpotent or super-potent;

- Lack active ingredients;

- Contain harmful or cross-reactive impurities;

- Lack or impede traceability; or

- Be made or packed in unsuitable conditions." (18)

The Pharmaceutical Research and Manufacturers of America (PhRMA) uses the same definition of counterfeit medicine as the WHO. In addition, PhRMA considers a "genuine product that has expired and has then been fraudulently relabeled" to be counterfeit. (19)

For more definitions of counterfeit drug, see *Annex 1*.

*Factors contributing to the manufacture and distribution of counterfeit (fake) drugs*

Medicines are high value products; demand for these items is endless. Production cost of fake drugs can be very low because cheap substitutes or none at all, are used; neither huge infrastructures nor facilities are needed; and there are no expenses incurred for quality assurance or meeting GMP requirements.

There are several factors contributing to the production of fake drugs: (15, 20, 21)

1. Lack of political will and commitment
   Drugs are used for the purpose of improving health. This makes them different from other consumer goods. The development, manufacture, import, distribution, and use of drugs require special knowledge and skills. Drugs should conform to the standards set for them and their quality should be strictly controlled. Meeting such requirements calls for a government with strong will and commitment to set up and operate a strong national drug regulatory authority.

2. Lack of legislation prohibiting counterfeiting of drugs
   In the absence of legislation and regulations for the proper control of medicines, counterfeiting activity is not treated as a criminal offense. For developing countries with existing national legislation, the sanctions imposed on counterfeiters are often not deterrent, which thereby encourages counterfeiters to carry on illegal activities because there is no fear of being caught and prosecuted by law. In India, for example, the penalty for a spurious drug manufacturer under the Indian Drugs Act is imprisonment of not less than three years and a fine of R 5000 (about US$ 100).

3. Absent or weak national drug regulatory authorities
   A competent national drug regulatory authority (NDRA) with adequate human and other resources is necessary in order to ensure that the drugs for human consumption are safe, effective, and of good quality. NDRAs should be able to control the manufacture, importation, distribution, and sale of medicines. The WHO reports that of 191 member countries, only 20% have well-developed drug regulation. Of the remaining countries, about 50% implement drug regulation at different levels of drug development and operational capacity, while the remaining 30% either have no existing drug regulation or, if there is any, a very limited

capacity that barely functions. For NDRAs to be competent and efficient, it is necessary for them to have adequate resources for drug regulation activities as well as for training personnel.

4.  Weak enforcement of drug laws and weak penal sanctions
    Strong enforcement of enacted deterrent anticounterfeiting laws is important in curbing this crime; otherwise, counterfeiters will continue this illegal activity because there is no fear of apprehension and prosecution.

5.  Shortage or erratic supply of drugs
    When demand for medicines exceeds supply, criminals take advantage of the situation by producing fake medicines as a substitute for the authentic ones. Inappropriate use of medicines by consumers also increases that demand. An example is the misuse of creams containing steroids used for skin bleaching and of body-building medicines that led to the production of counterfeit steroid-containing medicines distributed through unauthorized channels.

6.  High cost of medicines
    When the cost of medicines is high, there is a greater incentive for counterfeiters to produce fake drugs. For them, the cost of manufacturing is low and the potential profits high.

7.  Inefficient cooperation among stakeholders
    Cooperation among the regulatory authorities, police, customs services, and the judiciary is necessary in order to have effective control of the national drug market and enforcement of drug regulation. Inefficient cooperation results in counterfeiters escaping detection, arrest, and penal sanctions; it results in the inability of NDRAs to take countermeasures. Equally important is the cooperation of the pharmaceutical industry, wholesalers, and retailers to report to the NDRA cases of counterfeit drugs.

8.  Lack of control of drugs for export and within free trade zones
    Pharmaceuticals for export are not regulated by many exporting countries to the same standard as those manufactured for domestic use. Drug control is lax in free trade zones where repackaging and relabeling occur. This makes it easy for counterfeiters to introduce fake drugs into the distribution chain.

9.  Trade involving several intermediaries
    Trading of pharmaceuticals most often takes place through one or more intermediate countries or trading houses; rarely does it happen between the manufacturing country and the importing country. In trading houses, repackaging and relabeling may occur without any controls under conditions that do not conform to GMP requirements.

10. Corruption and conflicts of interest
    The existence of corruption and conflicts of interest strongly affects the efficiency of the drug regulatory authority as well as the law enforcement agency. This leads to a failure to arrest, prosecute, and convict those responsible for acts of counterfeiting.

**Consequences of using poor quality drugs**

Use of poor quality drugs bears serious health implications such as treatment failure, adverse reactions (7, 8), drug resistance (22), increased morbidity, and mortality. (23, 24) It can erode public confidence in a country's health program and waste scarce resources. (13, 25)

Counterfeit drugs can damage public trust, resulting in reduced investment in the pharmaceutical industry. It also can severely affect the business of the manufacturer whose products are being copied through loss of confidence as well as revenue. (26)

*Reported Cases*

Numerous reports in the press recently recount the use of spurious drugs resulting in serious and sometimes fatal consequences; such news is an indication that this major problem is gaining recognition worldwide.

On February 21, 2002, the *Far Eastern Economic Review* reported on the use of a fake version of a traditional Chinese medicine called HuangBai that was mixed with dangerously high amounts of an expired international antibiotic. This resulted in one person left in coma and 70 others severely poisoned. (27)

In September 2002, the *San Francisco Examiner* reported on a patient in China who died after albumin was administered intravenously by the physician. Police found the albumin bottle counterfeit. It was falsely labeled to look like a local Chinese pharmaceutical brand but contained an unknown liquid that proved fatal in the human bloodstream. In the same year, drug quality problems in China's pharmaceutical industry gained international attention when five women in Japan and Singapore died and 60 more became sick after taking Chinese-made diet pills. In 2001, the *Shenzhen Evening News* reported 192,000 deaths in China with the use of bogus or poor quality drugs. (28)

On November 17, 2001, the *South China Morning Post* reported that, based on the Shanghai Drug Administration figures for the year 2000, the estimated loss of life in China due to defective medicines is between 200,000 and 300,000 per year. Patients who are severely affected, but did not die, because of counterfeit and substandard drugs number in the millions. The Shanghai Drug Administration estimates that more than 2.5 million people were harmed in 1999. Based on anecdotal reports, about 10 to 30% of hospital patients suffer from an adverse drug reaction. (27)

On May 26, 2000, the *South China Morning Post* reported that fake antimalarials (mefloquine and artesunate) killed at least 30 people in Cambodia in 1999. The National Centre for Malaria found no medicinal value in the marketed fake antimalarials. (29)

On July 4, 1995, Reuters reported on more than one million Chinese children who became deaf and dumb as a result of using fake and/or substandard antibiotics to treat childhood colds and earaches. (27)

Between April and June 1998 in India, 36 children under the age of six contracted unexplained acute renal failure; 33 died despite peritoneal dialysis and supportive treatment. Subsequent investigation determined that locally manufactured "cough syrup" contaminated with diethylene glycol had been administered to the children. (30)

**Assessment of drug quality**

During the development of a new drug product, the manufacturer conducts detailed chemical studies on raw materials, synthetic intermediates, the drug substance itself, and the final formulated product. These studies identify the types and level of impurities, degradation products and rates, and appropriate analytical methods for monitoring these factors. Information gathered from these studies is used to identify potential sources of safety problems of the product, to meet the requirements of local and foreign regulatory agencies, and to serve as a basis for establishing quality control procedures and specifications for the drug product. (31)

The analytical tasks required in the development and marketing of a drug product can be summarized as follows: (31)

- Determination of identity and purity of starting materials and intermediates used in the manufacturing of the drug substance;

- Determination of the identity and purity of the drug substance;

- Isolation and identification of trace impurities in the drug substance;

- Determination of degradation rates and products for the drug substance;

- Determination of identity and purity of excipients used in manufacturing formulated products;

- Determination of degradation rates and products for the formulated drug;

- Establishment of an analytical reference standard for the drug substance.

Drug quality is assessed by compliance with pharmacopeial specifications. The procedure is carried out by qualified analysts (graduate in pharmacy, analytical chemistry, microbiology, or other relevant subjects) in national laboratories and quality control laboratories of drug manufacturers. It is done pre- and post-marketing of the drug using quality standards found in official pharmacopeias and standards and following analytical methods or techniques developed by the supplier. (32)

USP, the recognized standard-setting authority for pharmaceuticals (prescription products, over-the-counter (OTC) products, dietary supplements, other health-care products) in the U.S., adheres to a set of tests to assure quality, purity, strength, packaging, and labeling for each drug. The identity, strength, and stability are the components most commonly checked for drug quality control purposes using different tests according to specific USP-National Formulary (NF) monographs. (33) The USP-NF monographs are supported by Reference Standards materials that serve as quality control resources for the pharmaceutical industry.

*Quality control in developing countries*

An appropriate screening procedure or simple first-line test should identify the active ingredient of the drug. Depending on the country's existing capabilities and available resources, such tests as test-tube color reactions, melting point determination, or thin layer chromatography (TLC) can be used. These tests provide only an estimate of the amount of the drug substance, however, and could not detect and quantify other ingredients, which may be

harmful. The WHO suggests that screening procedures be conducted according to a consistent method; the tests should have sufficient sensitivity and specificity to allow precise testing of a large number of pharmaceutical products. (15)

According to USP DQI, there are two factors that contribute to the need for introducing simple basic tests to countries with limited resources: (32)

- The increasing threat of "bad quality drugs" in the marketplace; and

- The lack of drug quality control systems and advanced laboratories for drug quality assurance at various levels of drug management in poor countries.

*Three-Level Testing System*

USP DQI recommends the following three-level testing for drug quality: (34)

1. Basic tests for detection of substandard/counterfeit drugs (visual/physical inspection, colorimetric, simplified disintegration, and TLC);

2. Tests for authenticity in order to determine legal compliance and regulatory decision support (instrumental testing methods such as advanced TLC, high performance liquid chromatography [HPLC], gas chromatography [GC], ultraviolet [UV], etc.), in accordance with established or approved and validated techniques or methods in pharmacopeial monographs;

3. Comprehensive (but with specificity and selectivity) tests to determine unusual impurities and bioavailability/bioequivalency (BA/BE) studies.

For more discussion on the assessment of drug quality, see *Annex 2*.

## II.    OBJECTIVES

This paper reviews the drug quality based on the available information in 11 Asian countries with focus on anti-infective drugs in order to more fully understand the extent of the problem of poor drug quality, to identify gaps in quality assurance regionally and within countries, and to point the way toward addressing the issues.

## III.    METHODOLOGY

USP conducted a literature search and collected what is known about drug quality in eleven Asian countries. Studies and reports reviewed included journal articles, research reports, news reports, internet reports, conference proceedings, and newsletters.

**MAP**



**ASIA-Near East Region**

## IV. RESULTS

**BANGLADESH**

*Drug quality regulation/enforcement*

      A national drug policy and drug control ordinance was established in 1982 in Bangladesh. Among the provisions of the ordinance is punishment by imprisonment or fine for those who manufacture or sell substandard drugs. Enforcement of these laws, however, is weak. (35) In a 1992 report, it was mentioned that the Bangladesh Drug Administration had an annual budget of $250,000. It had 134 staff members, 43 of whom are assigned to inspection, licensing, and testing. (36)

*Drug quality data*

      In a survey conducted during 1988-91, it was found that 66 of the 198 licensed manufacturers were each producing between 1 and 16 substandard drugs (49% OTC drugs and 6.3% injectables, the remainder being non-injectable prescription drugs). Of the OTC products, about 36% was paracetamol and 41% consisted of antacids. The content of the active ingredients was found to be insufficient. (35)

      In 1992, quality studies were conducted on paracetamol tablets, ampicillin capsules, cotrimoxazole tablets/suspensions, vitamin B-complex tablets/capsules/injectables, and vitamin B-2 tablets. A total of 137 brand samples of these drugs were obtained from retail shops in various parts of the country and analyzed for level of content of the active ingredients as well as the disintegration of tablets. Results showed 37 samples were substandard, all manufactured by small companies. Of the 16 brands of paracetamol tablets and 10 brands of ampicillin capsules that were substandard, 11 and 8 respectively, had previously been considered

substandard in an assessment conducted by the regulatory authority. This holds true also for the two brands of cotrimoxazole suspension found to be substandard. All analyzed products for 13 of the top 15 companies in Bangladesh met the required standards. (35, 37, 38, 39)

A recent case study involving a sample of 15 brands of ciprofloxacin collected for chemical assay by HPLC and bioassay revealed seven brands containing active ingredient less than the USP specification. (40)

## CAMBODIA

*Drug quality regulation/enforcement*

According to a recent country study, counterfeit drugs are in circulation despite the pharmaceutical laws and regulations developed by the Ministry of Health. The laws enacted are weakly enforced due to a number of complicating factors: A poor public educational campaign to increase awareness of the problem; the general poverty throughout the country; a lack of trained drug inspectors and an inadequate budget to implement regular inspections; common corruption among authorities; and a lack of political will and cooperation. (41)

The Department of Drugs and Food (DDF) is the regulatory agency under the Ministry of Health mandated to ensure the safety, efficacy, quality of drugs and devices, and safety and quality of food and cosmetics. (41)

In the private sector, drug distribution involves the pharmaceutical importers, wholesalers, and private pharmacies. A WHO study reports that as of October 2000, there were 892 licensed pharmacies and 2800 unlicensed outlets, where most of the counterfeit drugs were obtained. In 1999, the Ministry of Health set up an Inter-Ministerial Committee to combat the pharmaceutical anarchy with goals of strengthening the management of the licensed pharmacies and eliminating the illegal outlets. Such efforts were unsuccessful owing to the lack of collaboration among concerned regulatory agencies. (41)

Cambodia has one joint-venture pharmaceutical industry with China. Along with six other private pharmaceutical companies, they produce oral dosage forms, which represent only 5 to 10% of the need in medicines for the whole population. Most of the pharmaceutical needs are covered by import products with an estimated annual cost of US$12 million. (41)

In the public sector, drug distribution has been done through the Central Medical Store of the Ministry of Health. It distributes the drugs to all 73 referral hospitals and more than 700 health centers throughout the country. (41)

Drug procurement is also carried out through the centralized system. However, the Ministry of Health plans to change this policy to decentralize the procurement system to a lower level and create a Government Purchasing Center. (41)

Trainings, workshops, and surveys on drug management and drug use at the central and provincial levels are organized by the Essential Drug Bureau. (41)

The change in the social economic system in 1993 resulted in a corresponding change in the pharmaceutical business. Regulations have been issued and implemented, such as: (41)

- National Drug Policy — which ensures the availability of safe, effective, good quality drugs at affordable prices to the population and rationalizes the supply and use of drugs throughout the country.

- Drug registration — considered a measure to combat counterfeit drugs. Only products registered by the DDF are authorized to be imported, manufactured, sold by retail pharmacy, displayed, and dispensed under the conditions specified in the license granted to undertake such activities. Products covered are both imported and domestic found in both private and public sectors.

- GMP guidelines

- Drug inspection — Drug controllers from the Legislation section of the DDF Drug Regulation Bureau conduct regular inspection of the retail pharmacies, import companies, and wholesalers. Currently, there are eight controllers at the central level and one or two at the provincial and district levels. Not all controllers have pharmaceutical expertise. Because of lack of competence and expertise, GMP certificates have not been issued to local manufacturers. Inspection of storage facilities of drugs in the public and private sector is being planned. Stronger measures are being called for to control and to close illegal pharmacies.

- Quality control — The National Quality Control Laboratory conducts tests on drugs from all sources that are submitted to the Ministry of Health for registration. Testing ensures the safety, efficacy, and quality of the drugs to be used by patients. Capacity of this laboratory is limited, however, due to lack of human resources and testing equipment.

- Other regulations — deal with licensing of pharmacy, import-export companies and distribution of pharmaceuticals; management and storage of pharmaceuticals; management of toxic-dangerous drugs; and the national essential program.

*Drug quality data*

The WHO-funded Ministry of Health survey on counterfeit and substandard drugs conducted by the Committee for Research and Study on Counterfeit Drugs in 2000 collected random sample products from Phnom Penh markets and the five provinces of Kampong Cham, Kampong Chhnang, Takeo, Kampong Speu, and Kandal. (41) A total of 230 samples were collected. The preparations included ampicillin 250 mg and 500 mg, amoxicillin 250 mg and 500 mg, bromhexin 4 mg and 8 mg, ciprofloxacin 500 mg, cephalexin 500 mg, cotrimoxazole 480 mg and 960 mg, chloramphenicol 250 mg, cimetidine 400 mg, dexamethasone 0.5 mg, diazepam 5 mg, erythromycin 250 mg, griseofulvin 500 mg, ibuprofen 400 mg, indomethacin 25 mg, loperamide 2 mg, metronidazole 250 mg, norfloxacin 400 mg, ofloxacin 200 mg, paracetamol 500 mg, ranitidine 300 mg, rifampicin 300 mg, tetracycline 500 mg, and vitamin C 500 mg. Of the 230 samples, 101 samples were submitted to the National Quality Control Laboratory and 129 were sent to the Drugs Analysis Division of Thailand for testing

identification, contents of active ingredients, and weight variation in accordance with the specifications set out by the British and the U.S. pharmacopeias. Other findings include:

- Of the 230 samples, 115 (50%) were found to be unregistered.

- These 115 samples were sent to the drug regulatory authority of the country of origin where 46 were confirmed to be genuine and 69 failed to reply. Among the 46 confirmed samples, three (6.52%) failed the test; among the 69 samples with no reply, three (4.34%) failed the test.

- Of the 230 samples, 30 (13.04%) failed quality testing: 24 (10.43%) were considered counterfeit (failed the test and not registered) and 6 (2.61%) were considered substandard (failed the test but registered).

The results showed that even in genuine products, as claimed by the manufacturers, (3 of 49) still failed the quality test. The laboratory investigation of drug quality will have to be carried out through a collaborative effort with the drug regulatory authorities of the country of manufacture and the manufacturers. (41)

The study demonstrated that regulatory measures such as drug registration can reduce the availability of counterfeit and substandard drugs. Among the 115 registered samples, only six (5.21%) failed the test; 24 samples (20.86%) of 115 unregistered also samples failed the test. (41)

Although the study showed that the prevalence of counterfeit drugs was only 13.04%, it is believed that the figure could be higher because people who live in the remote areas choose to buy their medicine from small illegal drug outlets that abound throughout the country (2800 unlicensed outlets). Stricter controls should be enforced at the points of entry because counterfeit and substandard drugs are more of a cross-border problem than a local problem (no domestically produced sample failed the test). (41)

In 1999, antimalarial drug samples in Cambodia were collected and sent for analysis to the drug analysis division of the Department of Medical Science, Ministry of Public Health, in Thailand. Results were double-checked in the laboratories of the supposed manufacturers of mefloquine in Australia and of artesunate in Guilin, China. Most of the bottles containing mefloquine and about half of the artesunate blister packs samples were fakes. At the end of 1999, a follow-up survey assessed the availability of fake drugs consisting of a total of 242 drug vendors and pharmacies from 12 different marketplaces, 133 were randomly selected for this study. The result of this investigation revealed that fake artesunate was being sold by 71% (86% sold the genuine drug) of drug vendors and pharmacies and 60% (61% sold the genuine drug) sold fake mefloquine. (4)

Another study showed 36 of 128 anti-infective drugs tested for quality were substandard; six had no active ingredient in the product. (42)

In a case study, a total of 132 samples of 14 different tracer drugs (amoxicillin, artesunate, ciprofloxacin, cotrimoxazole, doxycycline, erythromycin, mebendazole, mefloquine, praziquantel, quinine, rifampicin, isoniazid, tetracycline, diphtheria-pertussis-tetanus [DPT] vaccine, and zidovudine) were tested for quality. Results showed the following percentage of medicines were substandard: 13% from public facilities; 7.7% from

nongovernmental organizations (NGOs)/mission facilities; and 9.6% from private retail outlet. Overall, 12.4% of the samples failed the assay test and 7.1% failed the dissolution test. (43)

Cambodia participated in a 1999-2000 survey conducted by Newton P et al on the quality of artesunate tablets collected from shops, pharmacies, NGOs, and hospitals from five Asian countries (see *Multi-country studies*). The proportion of fake artesunate in Cambodia was reported to be 25%. (44)

## CHINA

*Drug quality regulation/enforcement*

China has more than 6300 drug manufacturers capable of producing more than 1350 types of chemical-based drugs and more than 8000 types of traditional Chinese herbal medicines (TCM). In 2000, the Chinese pharmaceutical industry output was reported to exceed US$ 28 billion. (27)

According to PhRMA, while it takes international companies about 10 to 15 years to develop a drug at an average cost of US$ 820 million, copying the drug takes only three to five years at an approximate cost of US$ 60,000 –120,000. PhRMA further reports that an estimated 10 to 15% of annual revenue is lost every year in China due to counterfeit drugs (industry loss of about US$ 3 and US$ 5 billion). Recent research reports indicate that nearly 97% of all international products made in China are reproduced by local Chinese companies. Most of these drugs are protected under foreign patent laws. For pharmaceutical products, 99% of the 3000 varieties of medicines made in China since the 1950s are imitations. (27)

Producing counterfeit drugs is a very attractive activity in the poorer areas of China. Some farmers in Guangxi Province were discovered to be making medicines out of the substances that are found around their farms, including animal feed, for as little as one RMB. They then sold the medicine for RMB 150 (US$ 18). The standard production run was for 2000 tablets. One production run brought in more money to the farmers than they made in one year. (27)

Because of this problem of counterfeit drugs, the Chinese government drafted and passed new pharmaceutical regulations on December 1, 2001. The State Drug Administration (SDA) is the main government agency responsible for regulating and administering these pharmaceutical laws. (27)

The SDA was created in 1998 as part of the central government's attempt to streamline bureaucracies and to consolidate the various health care regulatory functions under a single authority. The State Economic and Trade Commission (SETC) has the responsibility for administering drug-producing companies, and the Ministry of Health oversees hospitals and healthcare institutions. (27)

The SDA assumed some of the functions of the Ministry of Health and the State Administration of Traditional Chinese Medicine. Its responsibilities included supervising the research, production, distribution, and use of pharmaceutical products; conducting clinical drug research and monitoring adverse drug reactions; and registering new drugs, generics, imported

drugs, and TCM. The SDA has a wide variety of functions; however, it often lacks the staff it needs to implement its tasks. Its areas of jurisdiction include the following: (27)

- Drafting regulations on drug management, distribution, prescriptions, OTC purchase, and TCMs;

- Drafting quality management standards for drugs and medical devices, drug production, marketing and preparation for medical units, and for non-clinical research and clinical experiments;

- Drafting catalogs for medical devices, state basic medicines, and OTC medicines;

- Registering new and imitation drugs, imported drugs, TCMs that are under protection, imported medical instruments, and licensed pharmacists;

- Issuing production licenses for medical instruments and drug manufacturers;

- Formulating qualification certification systems for drug wholesale and retail enterprises as well as licensed pharmacists;

- Examining drug reappraisal requests;

- Monitoring adverse reactions, clinical experiments, and clinical pharmacological bases;

- Ensuring quality control and product safety certification of medical instruments and drugs;

- Guiding the work of the national drug inspection institutes;

- Punishing those who make fake or poor quality drugs;

- Supervising the management of TCM materials markets, anesthetic and psychoactive drugs, toxic drugs, and radioactive drugs; and

- Examining medicine advertisements.

The SDA adopted new rules on pharmaceutical registration and approval procedures. It formulated regulations governing drug imports and protecting the intellectual property of new drugs and establishing drug standards and a certification scheme for pharmacists. It tightened regulations on medical devices, drug packaging, and labeling. The SDA introduced new compliance guidelines for GMP certification for medical products, amended the Good Clinical Practice (GCP) standards for drug trials, issued the Good Laboratory Practice quality control code for non-clinical drug safety research, and formulated measures for the registration of drug research institutions. (27)

China's extensive subsidies for hospital-prescribed drugs had become an unbearable burden for the state, as hospitals relied on the high prices of medicines in their pharmacies to compensate for medical services that were provided at low cost. In order to control the state budgets, the government urged hospitals and healthcare centers to "buy local," since locally manufactured drugs were always cheaper than imported drugs. All these new regulations and the tightening of hospital budgets have resulted in an increase in the demand for counterfeit drugs. (27)

*Drug quality data*

According to the SDA, a nation-wide survey on the quality of medicines carried out in 1998 found that 13.1% of the 20,000 batches tested were either counterfeit or fell below minimal pharmaceutical standards. (45)

In 1997, *China News Digest* reported that the Health Ministry of China inspected 1100 medicines and found 138 products that failed to meet national standards. Of these, 48 were fake medicines with pirated registration numbers. (46)

At the 2002 Global Forum on Pharmaceutical Anticounterfeiting held in Geneva, Switzerland, a representative from the Glaxo SmithKline (GSK) pharmaceutical company reported on the counterfeiting of two of their products in China. The first was Imuran© tablets. The counterfeit Imuran© was found to contain the correct amount of azathioprine, the active ingredient; however, the tablets were labeled incorrectly as "azathiopring." Upon testing, the tablets failed the quality specification for disintegration time. The tablets were still intact after four hours in water at 37 °C, while genuine tablets dissolve in 45 minutes. The other drug was Zinacef© tablets. The genuine oral dosage form contains cefuroxime axetil; the counterfeit Zinacef© tablets revealed the presence of cefuroxime sodium, the injectable dose form. When taken orally, cefuroxime sodium is absorbed minimally by the digestive system resulting in no therapeutic benefit. (47)

## INDIA

*Drug quality regulation/enforcement*

"Counterfeit drugs could be the single biggest problem in India in the next ten years due to the growth of garage-based drug manufacturing outfits, rampant corruption, and weak drug control," according to R. Roychoudhury, president of the Delhi Society for the Promotion of the Use of Rational Drugs. The penalty for a spurious drug manufacturer under the Indian Drugs Act is imprisonment of not less than three years and a fine of R 5000 (about US$ 100). Such laws exist but they are rarely enforced. With over 20,000 manufacturers and inadequate staff to monitor the problem, as well as lack of laboratories and equipment for testing, the central and state regulatory bodies acknowledge that it is impossible for them to control the proliferation of substandard and counterfeit drugs without the active participation of the industry and traders. One important thing to note is that this illegal drug business seems to have strong political support. In September 2000, the pharmaceutical control authorities raided the Sitamarhi district of Bihar, which resulted in four arrests. The greatest resistance to this action came from people who have a strong influence on Members of Parliament. (48, 49, 50)

*Drug quality data*

A 2003 Scrip report estimated that 15 to 20% of the medicines sold in the country are counterfeits. (51) A case study reported in a 2001 conference showed the following percentage (out of 125 tracer medicines) that failed quality testing: 6% from the public sector, 12.7% from the private sector; and 0% from NGOs. (52)

In 2001, *Lancet* reported that, according to WHO statistics, India produces as much as 35% of the fake and substandard drugs in the world. A powerful group of manufacturers have taken over much of the production during the past three years. It is reported that these

counterfeit drugs are manufactured mostly in the northern states; but these fake drugs are widely available throughout the country. They are available as well in Myanmar (Burma) and Cambodia, and their distribution may even extend as far as the former Soviet states, as evidenced by the arrest of four Uzbek women caught trying to smuggle them to be sold in their country. (48, 49)

India was among the six countries that participated in a drug quality study which collected a total of 71 samples of the antituberculosis drugs isoniazid (INH) and rifampicin (RMP) as a single entity or a fixed-dose combination (FDC) (see *Multi-country studies*). Overall, 10% (4/40) of all samples obtained from all six countries, including 13% (4/30) RMP were substandard, containing < 85% of stated content. More FDCs, 21% (5/24), than single drug samples, 13% (2/16), were deemed substandard. (53)

## INDONESIA

### *Drug quality regulation/enforcement*

The Indonesian Drug and Food Control Agency (BPOM) reports that the problem of eliminating counterfeit drugs circulating in the country is due to the weak enforcement of the law. It suspects that bribery of unscrupulous law enforcers is a contributing factor to this problem as shown by the lenient punishment handed down by some judges in lawsuits against counterfeiters. (54)

### *Drug quality data*

BPOM reports that the most commonly counterfeited drugs are antibiotics, analgesics, and drugs for diabetes. In May 2003, BPOM discovered 55 counterfeit medicines being sold in the market. Among them were amoxicillin 500 mg capsules that contained only 45.84% and penicillin that contained 45.34% of the active ingredient. (54)

## LAO PEOPLE'S DEMOCRATIC REPUBLIC (PDR) or LAOS

### *Drug quality regulation/enforcement*

Lao PDR was established in 1975 at the end of the Indochina war. Later reforms resulted in the introduction of the New Economics Mechanism of 1985-86, which led to the rapid liberalization of private pharmaceutical businesses. Regulation of private pharmacies was introduced in 1988 and a National Drug Policy was adopted in 1993. (55)

The Ministry of Public Health has long been in charge of pharmaceutical matters. In 1983, there were three separate units set up comprised of pharmaceutical factories, the pharmaceutical center in charge of government procurement and distribution of drugs, and a new department of pharmacy. (55)

In 1990, a Food and Drug Administration Committee was established whose functions overlapped those of the department of pharmacy. Consequently, the two groups merged in 1994 to form the new Food and Drug Department (FDD). It consists of seven divisions, including one for drug control and one for inspection. As of 1997, there were 45 on staff: five in the drug control division and eight in the inspection division. The staff consisted of 28 pharmacists, one medical doctor, and four pharmacy assistants; most staff members finished their degrees in Laos where the curriculum is inadequate. Some continued their studies in the former Soviet

Union. For fiscal year 1995-1996, the FDD administrative budget was 40 million Kip or about US$ 57,000. The same set-up can be found at the provincial level and one person at the district level is responsible for FDD matters. The FDD issues licenses for class I and II pharmacies; the provincial health departments issue licenses for class III pharmacies. (55)

According to a 1995 report, about 70% of the 3000 pharmaceutical products in Laos were imported by 30 licensed pharmaceutical import companies; the remainder was locally produced. (56) These pharmaceutical products are dispersed into more than 2000 licensed private pharmacies (55), each of which is supposed to obtain their drugs from licensed companies and factories. Yet approximately 60% of drug sellers have also bought drugs from illegal sources. (57) Drugs are also distributed to public pharmacies attached to government health institutions. (55)

Between 1997 and 1999, Laos implemented the Quality Assurance (QA) system within the National Drug Policy Program (NDPP, adopted in 1993) that consisted of: (57)

- The development of regulations, e.g., improvement of the drug registration system and increased requirements for imported products;

- Training of drug inspectors in GMP and Pharmacy Practice, including storage conditions, followed by at least one inspection in all factories and two in each private pharmacy a year; and

- Appropriate legal action, e.g., imposition of fines and recall of products.

*Drug quality data*

From 1990 to 1993, the Drug Quality Control Center (DQCC) performed three studies to assess the quality of pharmaceutical products available in the country's market. (58)

The first study analyzed 502 samples of which 247 were evaluated in relation to drug registration and 168 in relation to post-marketing monitoring. Results of the laboratory tests showed 87 (17%) of the samples were substandard.

The second study analyzed 112 samples obtained from different provinces. Results of the laboratory tests showed 37 (33%) failed to meet quality standards: Of the 37 samples, 18 (49%) contained less than 50% of the amount of active ingredients.

The third study analyzed 25 samples. The results showed that the amounts of active ingredients contained were in the range of 0% to 95%. All the products found with no active ingredients were classified as counterfeit.

In 1995, a similar study was conducted on samples of pharmaceutical products obtained from the markets of different provinces in the country. Results showed several of the products to be substandard with some products containing no active ingredient at all. (59)

In a baseline study conducted in 1997, 46% of 366 samples of four different essential drugs (amoxicillin, tetracycline, chloroquine, acetylsalicylic acid [ASA]) obtained from 106 private pharmacies in the Savannakhet province were found to be substandard, but few were fake: 12 (3.3%) of the 366 samples had no active ingredient; 42 (11.5%) contained levels of active ingredient outside the pharmacopeial limits; 128 (35%) showed excessive weight

variation; and 4 (1.1%) resulted from poor pharmaceutical management (tetracycline capsules were found mixed with the ampicillin capsules). (60)

In 1999, the second part of the study (61) was conducted to assess the effect of regulatory intervention on private pharmacy services. (The quality assurance system within NDPP was implemented during 1997-99.) A total of 300 samples of the same essential drugs used in the first study were collected from 92 pharmacies. The samples were analyzed at the Food and Drug Quality Control Center in Vientiane using BP and USP specifications. Results indicated a significant decrease in the percentage of substandard drugs from 46% (169/366) to 22% (66/300) between 1997 and 1999 ($p < 0.001$). There was a significant reduction in substandard ampicillin and tetracycline from 67% to 9% and from 38% to 12%, respectively ($p < 0.001$), but no statistically significant improvement for chloroquine and ASA. There were only a few drugs that did not contain the active ingredient in both the 1997 and 1999 studies. Only 10 of the 98 ampicillin samples contained no active ingredient in 1997 and 2 of the 77 in 1999. The drug samples found with lower or higher content of active ingredient than approved limits had decreased from 12% in 1997 to 4% in 1999 ($p < 0.001$). The weight variations outside the approved limits had decreased from 35% to 14% ($p < 0.001$) during the same time period.

In the 1999 study, 24% (23/97) of the drugs produced by the factories in Laos, 17% (24/143) of the drugs from Thailand, and 47% (17/36) of the drugs from unknown sources were substandard. The share of ampicillin produced in Laos was 71%, of which only two were substandard due to tablet weight outside the standard limits. Of the 34 substandard chloroquine samples manufactured by Laotian factories, 16 had tablet weight outside the standard limits; eight of 35 chloroquine samples from Thailand also had weight variation outside standard limits; one chloroquine sample from France had a very high level of active ingredient. All nine ASA tablets from Thailand had level of active ingredient outside the standards limits. In 1997, 28 of the 54 drugs with no active ingredient or an active ingredient below or above the standard limits could be traced; 20 of these came from local factories — five from Thailand, and three from Vietnam. The authors of this study attributed the improvement in drug quality to the development and enforcement of the QA system within NDPP. Yet, despite this improvement, the authors still consider the prevalence of substandard drugs (22%) unacceptably high. (57)

Lao PDR participated in a 1999-2000 survey conducted by Newton P et al on the quality of artesunate tablets collected from shops, pharmacies, NGOs, and hospitals from five Asian countries (see *Multi-country studies*). The proportion of fake artesunate in Laos was reported to be 38%. (44)

## MYANMAR (BURMA)

*Drug quality regulation/enforcement*

According to a WHO study (13), the total public sector drug expenditure in 1994-95 was US$ 6.5 million. The total value of drug imports during the same period was US$ 0.9 million. At the time the WHO study was done, Myanmar had 146 pharmacists, one state-owned pharmaceutical industry, about 60 private small scale pharmaceutical industries, 20 importers, and 275 wholesalers. The public sector offered 144 drug outlets and the private pharmacies numbered about 8500. As of 1995, there is a total of 1600 registered products.

Drug shops located in marketplaces had proliferated in the country over the years. Some drugs sold were of unknown quality, safety, and efficacy; either these drugs were imported or smuggled into the country through unauthorized channels. (13)

Authorized manufacturing, importation, and distribution of drugs are conducted by both the public and private sectors. In the public sector, three Ministry departments are involved: Health (MoH), Trade and Commerce, and Industry. The Central Medical Stores Depot (CSMD) of MoH imports drugs and distributes them to government hospitals and health care facilities. Most of the drug supplies from CSMD are purchased from the sole state-owned pharmaceutical company, the Myanmar Pharmaceutical Factory, which is under the Ministry of Industry. The Medicines and Medical Equipment Trading (MMET), under the Ministry of Trade and Commerce, imports drugs and distributes them to the public and to private clinics. (13)

None of the 60 small-scale private manufacturers had licenses issued by the MoH to manufacture drugs; however, their products were sold in the market. It was also noted that neither state-owned nor private industries comply with GMP requirements. Manufacturing was carried out using inappropriate machines and under extremely unhygienic conditions. There was no quality control laboratory or any means of quality assurance. Activities were managed and operated by people with no qualifications or training in pharmaceutical production or quality control. (13)

In 1972, the Public Health Law, which served as the legal instrument for drug control until 1992, was enacted but it contained no specific activities related to the exercise of regulatory control on importation, manufacture, and distribution of drugs. In 1991, the country adopted a National Drug Policy (NDP) with objectives that include ensuring the availability of effective and safe drugs of good quality. In 1992, the National Drug Law was enacted and, in 1993, regulations for enforcement were issued by the MoH. The drug law and regulations included importation, manufacture, distribution, drug registration, inspection, and quality control of drugs. The drug law also defined "fake drugs" and "drugs differing from standards," which are prohibited. (13)

The three authorities responsible for the enforcement of the drug law are: (13)

- The Myanmar Food and Drug Board Authority (MFDBA), under the MoH, provides guidance on the implementation of the NDP and establishment of the Food and Drug Supervisory Committees (FDSCs) at the central level, as well as in the states/divisions, districts, and townships;

- The State/Division Food and Drug Supervisory Committees under the Director-General of the Department of Health (also the chairman of the Central Food and Drug Supervisory Committee (CFDSC), license drug wholesalers and retailers;

- The CFDSC licenses the local drug manufacturers and gives drug importation approval certificates to importers. At the township level, the FDSCs are managed by the Township Medical Officers. The committees include the Township Medical Officer, the Commander of the Police, and the representatives of the City Development Committee and the General Administration Committee.

License applications are submitted to the respective Township Food and Drug Supervisory Committee, which inspects the shop and refers them to the State or Division Food

and Drug Supervisory Committee for a decision. Licenses are issued by the Township Medical Officer based upon the decision by the State or Division Food and Drug Supervisory Committee. (13)

In 1995, the Food and Drug Administration (FDA) was established with the following responsibilities: Issuing marketing authorization for pharmaceuticals, inspection of manufacturing plants and importers, and testing the quality of drugs. It has a Drug Advisory Committee (DAC) that evaluates and registers drugs. Registration is required for imported and locally manufactured products for both the public and the private sectors. At the time of the WHO study, more than 50% of the drugs in the market, including those domestically produced, were not registered by the FDA. (13)

Inspection of manufacturing plants is conducted by two FDA inspectors. The agency has a non-descriptive checklist of GMP requirements for manufacturers. Companies owned by Myanmar nationals are expected to meet only part of the requirements, as opposed to foreign companies who are obliged to meet all of them. There were no standard procedures for inspectors to follow. The WHO study noted that the number of inspectors is inadequate and they also need training and experience in GMP inspection. (13)

Inspection of the drug distribution channels is the responsibility of the FDSC at the various levels. However, inspection is truly done only at the central level where services are not fully operational and inspections are rarely conducted. The committee members do not have the pharmaceutical expertise. There is no post-marketing surveillance. The WHO study mentioned that drugs get into the country through illegal channels. Tampering of labels as well as transferring products from one container to another are common practices. In some marketplaces, expired drugs, drugs without expiry dates, and drugs without names of manufacturers were still being sold. (13)

The drug law requires distribution channels to be supervised by technically qualified persons. The WHO survey noted that most distribution outlets were being managed by unqualified staff. The storage and distribution conditions were bad and in need of drastic improvement. (13)

*Drug quality data*

The FDA quality control laboratory conducts quality testing on drugs for registration. The WHO study reported that very little analytical activity was done. Only 32 samples were tested in 1994-95, of which 8 (25%) did not meet quality standards. Three of the failed samples were substandard and 5 (15.6%) did not have the active ingredients. (13)

In the study conducted by WHO, two types of samples were collected. The first group consisted of 215 samples of the following drugs: amoxicillin, ampicillin, chloramphenicol, chloroquine, cotrimoxazole, metronidazole, ranitidine, rifampicin, tetracycline, plus paracetamol. These were purchased from public and private drug outlets and marketplaces in four cities. The second group consisted of 23 samples of products removed from their original primary containers and repacked in polyethylene plastic bags by the vendors and sold without labels. These preparations consisted of amoxicillin capsules, ampicillin capsules, tetracycline capsules, as well as vitamin B tablets, according to the vendors. These were tested at the WHO collaborating laboratory in Thailand and additional information was obtained from the DRAs of Myanmar to check whether or not they were registered. Unregistered products were sent to

the DRAs of the countries of manufacture. It was not possible to assess the second group of samples because they were not in their original containers. Of the 215 samples, only 92 (43%) were found to be registered with the FDA. (13)

Of the 215 samples collected, 212 were sent to the WHO laboratory in Thailand to determine identity and content of the active ingredients. Results showed 34 (16%) failed to pass the quality test with active ingredients below BP93 and USP23 limits. One sample contained the wrong ingredient. The content of active ingredient in six samples was in the range of 2% to 60% of the labeled amount. Chloramphenicol preparations showed a high failure rate (35%) followed by ranitidine (20%), cotrimoxazole (19%), and amoxicillin (16%). All tested samples had a shelf-life ranging from one to three years at the time of testing. (13)

For the drugs produced locally, the failure rate was 14%, while it was 16% for imported products. For non-registered products, both local and imported, the failure rate was 24%, while the failure rate was 6% for registered products. (13)

Of the 147 samples sent to the country of manufacture for investigation, 110 were confirmed to be genuine, five were mislabeled as to their source (although they contained the active ingredient as claimed in amounts within the pharmacopeial limits), and one contained the wrong ingredient. There were no replies received for the remaining 31 samples. Of the 110 genuine samples, five had active ingredients below the pharmacopeial limits, with the content ranging from 80% to 87% of the labeled amount. Of the 31 samples with no replies received, 10 (32%) were substandard with the content of the active ingredient ranging from 26% to 89%. It was not possible to determine whether these samples were genuine or not owing to the fact that no reply was received from the country of manufacture. (13)

Myanmar participated in a 1999-2000 survey conducted by Newton P et al on the quality of artesunate tablets collected from shops, pharmacies, NGOs, and hospitals from five Asian countries (see *Multi-country studies*). The proportion of fake artesunate in Myanmar was reported to be 40%. (44)

## PAKISTAN

*Drug quality data*

Estimates about the private sector in Pakistan suggest that 50% of the drugs in the market are counterfeit. (62)

At the Global Forum on Pharmaceutical Anti-Counterfeiting held in Geneva in 2002, the GSK representative reported finding the labels and components of Engerix B vaccine to be counterfeit. The vials did not contain the vaccine and the contents were not sterile. (47)

## PHILIPPINES

*Drug quality regulation/enforcement*

The Philippine Department of Health, the Bureau of Food and Drugs, and the local industry association of research and development-based companies are working together to raise awareness of the risks of counterfeit drugs and how to recognize them. (63)

*Drug quality data*

In a recent pharmaceutical news report, the Department of Health noted that up to 300 million pesos (US$ 6 million) worth of fake medicines are confiscated every year in the country. (That is less than 1% of the country's 50 billion pesos drug market and probably only a fraction of the total counterfeit market). Of the confiscated drugs, 80% are not officially registered while the rest do not meet state quality standards, and most were imported illegally from other Asian markets. (63)

In 2001, the Bureau of Food and Drugs found several drug outlets selling counterfeit drug products, including those not registered with the bureau. The most commonly found counterfeit branded drugs were: Appetens tablet, Ponstan capsule, Mosegor Vita tablet, Augmentin injection, Decilone-Forte tablet, Fortum injection, Propan with Iron capsule, Voltaren SR tablet, Inoflox capsule, and Verorab Injection. (64)

In 1995, the Philippines Counterfeit Action Program (Philcap) carried out a study involving 1359 samples bought from 473 drugstores. Results showed that approximately 8% of the samples tested were counterfeit. Approximately 11% of the drugstores visited were selling counterfeit drugs. Seventeen percent of the medicines obtained were imported illegally or diverted illegally into the country. Among the counterfeit medicines were cardiovascular, rheumatoid arthritis, osteoarthritis, asthma, anti-infective, and anti-inflammatory drugs. (64, 65)

**THAILAND**

*Drug quality data*

A recent WHO estimate suggests that in Thailand, 8.5% of all medicines on the market are substandard. (66)

In 1997, fifteen samples of chloroquine (tablets, oral syrup, injection), amoxicillin (capsules and oral suspensions), tetracycline (capsules and tablets), cotrimoxazole (tablets and syrups), and ampiclox (capsules, oral syrups, and suspensions) were collected in a controlled and methodical manner from several nonpharmacy outlets (n=10) and pharmacies (n=5). These were then analyzed using HPLC. Results showed 40% of samples had active ingredients outside the BP limits (about 50% of these were obtained from nonpharmacy outlets); three of five chloroquine samples had no active ingredient. (67)

Thailand participated in a 1999-2000 survey conducted by Newton P et al on the quality of artesunate tablets collected from shops, pharmacies, NGOs, and hospitals from five Asian countries (see *Multi-country studies*). The proportion of fake artesunate in Thailand was reported to be 11%. (44)

**VIETNAM**

*Drug quality regulation/enforcement*

A new economic policy called "doi moi" (economic renovation) was adopted by the Communist Party congress in 1986. This policy brought changes from a command economy to a free market economy, although many sectors were still being managed by the government.

These changes led to a considerable increase in the number of private pharmaceutical companies as well as a substantial increase in pharmaceutical imports. (13)

According to a WHO study report, the drug expenditure in the public sector in 1995 was approximately US$ 240 million. Local drug production account for about US$ 87 million and the total of pharmaceutical imports was US$ 195 million. There were 7500 pharmacists and 16,376 pharmacy technicians in the country. In 1996, a National Drug Policy (NDP) was established and among its objectives was to ensure quality in production, storage, and distribution of drugs. (13)

The pharmaceutical industry is divided into two groups. The first group is the state-owned manufacturing industries, which numbered 154 in 1995. Industries in this group are organized into 35 different companies under the direction of one corporation called the General Pharmaceutical Company, which is supervised by the Ministry of Health. These companies are involved in the manufacture, import, export, and distribution (wholesale and retail) of finished products and raw materials. (13)

The second group consists of 135 manufacturing plants that are owned by different provinces/cities and managed by the People's Committee of the respective province/city. Most of these companies are engaged in the distribution of pharmaceuticals and the manufacture of traditional medicines. A small number are involved in manufacturing and import-export activities. Further, the Ministries of Internal Affairs, Defense, and Transportation manage companies that manufacture and distribute pharmaceuticals. (13)

The Ministry of Health is responsible for drug regulation. The Drug Law regulates the manufacture, importation, and distribution of drugs. Three departments, the Drug Administration (formerly known as the Pharmacy Department), the Pharmaceutical Inspection Department, and the National Institute of Drug Quality Control, are charged with drug regulation and report directly to the Vice Minister for Pharmaceuticals. (13)

Registration is required for both imported and locally produced drugs. The Drug Administration coordinates and monitors the implementation of the NDP. Its other functions include developing drug legislation/regulations; registering drugs; issuing import-export licenses; controlling the manufacture, importation, promotion, and advertising of drugs; conducting post-marketing surveillance; and disseminating drug information. At the time of the WHO survey, it had about 20 staff members working in different sections. The Drug Registration Commission assists in the registration of drugs. Part-time experts help in evaluating drug submissions. At the time of the WHO survey, there were 8000 products registered. All locally manufactured products were registered; only 75% of drugs imported by the public sector were registered. The WHO study noted several unregistered drugs that were available in the market. (13)

Drug inspection is undertaken by both the central and provincial inspectors (two inspectors at the national level and one or two at the provincial level). As of 1995, the total number of inspectors was 61. Because the government emphasizes strengthening laboratory services rather than inspection services, no inspection is done at custom warehouses. As of 1996, no GMP guidelines or manuals for inspectors and manufacturers existed. It was reported, however, that Association of Southeast Asian Nations (ASEAN) GMP guidelines would be adopted. There were only a few manufacturing plants that complied with GMP requirements.

Most plants had old equipment and inadequate premises. Inspection was weak and rarely carried out. (13)

In the area of distribution, private outlets were reported to be tampering with labels and selling and dispensing drugs imported from unauthorized channels and counterfeit drugs. These included antibiotics, analgesics, vitamins, and traditional medicines. Inspectors have discovered mislabeled ampicillin, tetracycline, and phenoxymethylpenicillin. For the most part, inspection of these premises was ineffective and the number of inspectors was inadequate. (13)

In most wholesale and retail outlets, drugs were found in poor storage conditions and exposed to sunlight. Products in blister/strip packs were taken out of their secondary containers (boxes) and were displayed unprotected from sunlight. In most cases, package inserts were discarded. (13)

The system for quality control of drugs began in 1958. Quality control is conducted by the National Institute of Drug Quality Control in Hanoi, the Sub-Institute of Quality Control in Ho Chi Minh City, and the drug quality control laboratories in the provincial health departments. As of 1995, there were 701 staff members working in the two institutes and the provincial laboratories (42 with postgraduate degrees, 313 pharmacists, 212 technicians, and 134 administrative personnel). The two institutes are well-equipped compared to the provincial laboratories, which have basic equipment only. (13)

*Drug quality data*

Post-marketing surveillance is one of the activities undertaken by the institutes and provincial laboratories. In 1995, there were 31,125 drug samples collected from various parts of Vietnam and tested for quality; 1703 samples did not meet the quality standards. Of these, 1537 were substandard and the remaining 166 were counterfeit. The post-marketing quality surveillance system using the simple testing kits developed by the National Institute of Drug Quality Control helped decrease the rate of drug failure. (13)

In the study conducted by WHO, a total of 288 imported and locally manufactured samples were purchased from the public and private pharmacies and marketplaces in Hanoi, Ho Chi Minh City, Ha Long, and Hai Hung. These samples included the following antimicrobials: amoxicillin, ampicillin, chloramphenicol, chloroquine, metronidazole, rifampicin, and tetracycline. Non-antimicrobials included diazepam and paracetamol. Samples collected were sent to the WHO collaborating laboratory in Thailand. Additional information was requested from the DRAs of Vietnam to confirm whether the drugs were registered and genuine. Unregistered products were sent to the DRAs of the countries of manufacture. Of the 127 imported products, 51 (40%) were registered. All the locally manufactured products were registered. Consequently, of the 288 samples purchased, 76 (26%) were not registered. (13)

Results of laboratory testing showed that of the 288 samples collected, 21 (7%) products contained active ingredients below the labeled amount (60-89%), one contained active ingredients above the pharmacopeial limit, and the remaining 266 (92%) samples contained active ingredients within BP and USP limits. The failure rate was 8%. (13)

Of the 51 samples of imported registered products, 3 (6%) failed the laboratory test; of the 76 samples of imported unregistered products, 15 (20%) were found to contain active ingredients below the labeled amount. Of the 161 samples of locally produced and registered

drugs, only 4 (3%) failed the laboratory test. The failure rate was 20% for non-registered products (imported and locally produced) and 3% for registered products. (13)

A portion of each of 67 products of the 288 collected samples was sent to DRAs of country of manufacture. These were not registered products in Vietnam. Replies confirmed 53 samples to be genuine. There were no replies received for 14 products, therefore, it was impossible to confirm whether or not they were genuine. Of the 53 confirmed genuine products, 13 (19%) failed laboratory testing. The content of the active ingredients was found to be in the range of 60% to 89% of the label claim. These included antimicrobial products (amoxicillin, ampicillin, and rifampin). The 14 samples for which no replies were received had active ingredients within the BP and USP limits. (13)

In another study reported in 1998, samples of antimalarials were collected from shops and pharmacies in three provinces included in a previous survey and were assessed for content and expiration date by the Institute of Drug Quality Control in Vietnam. Results showed that only 3.2% did not meet the requirements for quality. However, when the 10% sample of drugs was independently assessed by WHO technicians, 70% of the samples failed to meet standard specifications. (68)

At the 2002 Global Forum on Pharmaceutical Anti-Counterfeiting held in Geneva, a GSK representative presented a report about the adulteration or reuse of components of Fortum injection, a GSK product. The hospital staff in Vietnam discovered adulterated product with the carton and labels showing staining, which indicated that they may have been salvaged from the waste stream. Upon removal of the plastic flip-off cap, puncture marks in the rubber plugs and yellow staining were noted, which meant that they were used previously and degraded residues were not cleaned off. Analysis showed the content to be streptomycin, a cheap and ineffective substitute for ceftazidime, the active ingredient of Fortum. (47)

Vietnam participated in a 1999-2000 survey conducted by Newton P et al on the quality of artesunate tablets collected from shops, pharmacies, NGOs, and hospitals from five Asian countries (see *Multi-country studies*). The proportion of fake artesunate in Vietnam was reported to be 64%. (44)

## V.    MULTI-COUNTRY STUDIES

In a 1999-2000 survey, Newton P et al collected artesunate tablets from shops, pharmacies, NGOs, and hospitals from five Asian countries (Cambodia, Laos, Myanmar [Burma], Thailand, Vietnam). In the study, 104 blister pack samples were obtained (Cambodia = 26, Laos = 8, Myanmar = 51, Thailand = 8, Vietnam= 11). These tablets were tested for authenticity using the Fast Red TR dye method. Some of the packages were also examined. Overall, 30 (29%) of these blister packs did not contain artesunate. Of the samples bought from pharmacies and shops, 39 (38%) were counterfeit. Fake artesunate was found in all five countries. These results were in complete agreement with the results of examining the packages of the 84 samples. The proportion of fake artesunate in Cambodia was reported to be 25%, Laos 38%, Myanmar 40%, Thailand 11%, and Vietnam 64%. (44)

India and Vietnam were among the six countries involved in a study on detecting substandard anti-tuberculosis drugs conducted by the U.S. Centers for Disease Control and Prevention (CDC). A total of 71 anti-TB drug samples of isoniazid and rifampin as single or

fixed-dose combinations (FDCs) were obtained from the National TB programs, hospital, and local pharmacies from the following countries (Colombia = 11, Estonia = 25, India = 22 from local pharmacies, Latvia = 8, Russia = 4, and Vietnam = 1 from a local pharmacy). These were analyzed by CDC and FDA using TLC and confirmatory techniques, using legal reference pharmacopeia methods (LRM), such as by HPLC and UV spectrophotometry. Overall, 10% (4/40) of all samples, including 13% (4/30) RMP were substandard, containing < 85% of stated content. More FDCs, 21% (5/24), than single drug samples, 13% (2/16), were substandard. (53)

**Table 1. Percentage of substandard/counterfeit drugs in 11 Asian countries based on studies/reports**

| Country | General Medicines/ Types of Drugs Tested | Results |
|---|---|---|
| Bangladesh | Ciprofloxacin | 7 (46%) of the 15 brand samples were substandard |
| | Paracetamol, ampicillin, cotrimoxazole, vitamin B2 and B complex | 37 (27%) of 137 brand samples were substandard |
| Cambodia | Ampicillin, amoxicillin, bromhexin, ciprofloxacin, cephalexin, cotrimoxazole, chloramphenicol, cimetidine, dexamethasone, diazepam, erythromycin, griseofulvin, ibuprofen, indomethacin, loperamide, metronidazole, norfloxacin, ofloxacin, paracetamol, ranitidine, rifampicin, tetracycline, vitamin C | Of the 230 samples, 30 (13.04%) failed quality testing of which 24 (10.43%) were counterfeit and 6 (2.61%) were substandard |
| | Anti-infectives | 36 (28%) of 128 samples were substandard |
| | Amoxicillin, artesunate, ciprofloxacin, cotrimoxazole, doxycycline, erythromycin, mebendazole, mefloquine, praziquantel, quinine, rifampicin, isoniazid, tetracycline, diphtheria-pertussis-tetanus vaccine, zidovudine | Of 132 samples, 16 (12%) were substandard and 9 (7%) failed dissolution test |
| | Artesunate | 25% counterfeit |
| China | State Drug Administration nationwide survey on the quality of medicines | 13.1% of the 20,000 batches tested were either counterfeit or substandard |
| | Health Ministry of China medicine inspection | 138 (12.5%) of 1100 medicines were substandard and 48 (4.36%) were counterfeit |

| Country | General Medicines/ Types of Drugs Tested | Results |
|---|---|---|
| India | Tracer medicines that included antibiotics, antimalarials, antiparasitics, anti-TB, etc. | failed quality testing: 6% public sector, 12.7% private sector |
| Indonesia | Indonesian Drug and Food Control Agency tested 55 counterfeit medicines to include amoxicillin and penicillin | Amoxicillin contained 45.84% of active ingredient and penicillin contained 45.34% of active ingredient |
| Lao People's Democratic Republic (PDR) | Drug Quality Control Center – three analyses of pharmaceuticals in the market<br><br>Amoxicillin, tetracycline, chloroquine, acetylsalicylic acid<br><br>Artesunate | 87 (17%) of 502 samples were substandard; 37 (33%) of 112 samples were substandard; 25 samples showed the amount of active ingredient were in the range of 0 to 95%.<br><br>46% of 366 samples were substandard; 22% out of 300 samples were substandard in a follow-up study, after implementation of quality assurance system<br><br>38% counterfeit |
| Myanmar (Burma) | Amoxicillin, ampicillin, chloramphenicol, chloroquine, cotrimoxazole, metronidazole, ranitidine, rifampicin, tetracycline, paracetamol<br><br>Artesunate | 34 (16%) out of 212 samples were substandard<br><br>40% counterfeit |
| Pakistan | Drugs in private sector | Estimated to be 50% counterfeit |
| Philippines | Anti-infectives, anti-inflammatory agents, drugs for cardiovascular disease, rheumatoid arthritis, osteoarthritis, and asthma | 8% of 1359 samples were counterfeit |

| Country | General Medicines/ Types of Drugs Tested | Results |
|---------|------------------------------------------|---------|
| Thailand | Chloroquine, amoxicillin, tetracycline, cotrimoxazole, ampiclox | 40% of the 15 samples were substandard; 3 out of the 5 chloroquine samples had no active ingredient |
|  | Artesunate | 11% counterfeit |
| Vietnam | Post-marketing surveillance of drugs | 1703 (5.47%) of the 31125 samples failed quality testing |
|  | Amoxicillin, ampicillin, chloramphenicol, chloroquine, metronidazole, rifampicin, tetracycline, diazepam, paracetamol | 21 (7%) of the 288 samples were substandard |
|  | Antimalarials | 70% out of the 10% of the drug sample were substandard |
|  | Artesunate | 64% counterfeit |

## VI.   IDENTIFYING GAPS AND WEAKNESSES

Based on the information presented in the country studies/reports, the following gaps and weaknesses have been identified:

1. Weak national drug regulatory authority and weak enforcement of drug laws
   The national drug regulatory authority has limited capacity to function due to inadequate resources for drug regulation activities and training of personnel. Although drug laws exist, they are rarely or weakly enforced, such as in Bangladesh, Cambodia, and India. Implementation of activities is difficult due to budget constraints and inadequate staff to monitor the problem. Lack of budget often leads to corruption, which could affect enforcement of the law by failure to arrest and punish counterfeiters.

2. Little or no GMP compliance by manufacturers
   In Cambodia, owing to the lack of pharmaceutical expertise by drug inspectors, GMP certificates have not been issued to the drug manufacturers. In Myanmar, it was noted that none of the 60 small-scale private manufacturers had licenses issued by the MoH to manufacture drugs. It was also noted that neither state-owned nor private industries comply with GMP requirements. Manufacturing was carried out using inappropriate machines and under extremely unhygienic conditions. There was no quality control laboratory or any means of quality assurance. Activities were managed and operated by people with no qualifications or training in pharmaceutical production or quality control. As of 1996, Vietnam was reported to

have no GMP guidelines or manuals for inspectors and manufacturers, although there was a plan of adopting the ASEAN GMP guidelines. Only a few manufacturing plants in Vietnam were in compliance with GMP requirements. Most plants had old equipment and inadequate premises. Inspection was weak and rarely carried out.

3. Limited laboratory capacity in terms of qualified staff and equipment
The capacity of the national drug quality control laboratory to conduct quality testing of drugs is usually limited due to lack of qualified personnel and testing equipment, as in the case of Cambodia and Myanmar, wherein the WHO study noted that very little analytical activity was done at the FDA quality control laboratory; only 32 samples were tested in one year (1994-1995).

4. Lack of competent drug inspectors
Regular inspection is rarely implemented due to lack of competent and adequately trained inspectors, as seen in Cambodia, India, and Myanmar. Training on GMP and Pharmacy Practice including storage conditions is necessary. Lack of inspectors means less control of pharmaceuticals at points of entry. In Cambodia, for example, counterfeit and substandard drugs are more of a cross-border problem than a local problem. In Vietnam, no inspection is done at customs warehouses.

5. Lack of inexpensive, quality-assured drugs
Limited availability of low-cost genuine drugs helps promote counterfeiting. A good example is the adulteration or reuse of the GSK product, Fortum injection, in a hospital in Vietnam.

## VII. WHAT HAS BEEN DONE

Most of these countries have already stepped up their efforts to combat the widespread availability of poor quality drugs. Pakistan, for example, sought help from the WHO to set up a rational medicines network in reaction to concerns expressed by health care professionals there about a number of medicines of dubious quality being sold by irregular outlets, such as the village markets. The network raises awareness about the safe use and potential risk of medicines. (69)

China has increased inspections of companies suspected of producing counterfeit or substandard drugs, part of a wider overhaul of China's medical services that addresses the issue of overprescribing. The Ministry of Health plans to end the practice of "lengthy prescriptions." (45) Efforts have been intensified to crack down on smuggled raw ingredients for manufacturing drugs, reinforcing random testing of imported drugs, and tightening the regulation on drug advertising. (27)

China also has prohibited individuals from the wholesale trading of medicines at county-level pharmaceutical trade fairs where fake and substandard medicines abound. Those licensed to sell traditional Chinese herbs, however, are allowed. (27)

India's Ministry of Health and Family Welfare has formed an expert committee to examine regulatory issues and the dangers of counterfeit and substandard drugs. (70) This committee, which was formed in April 2003 (70), already has made some recommendations (see *India* under *Country-specific recommendations* section).

The Philippines formulated a special law on counterfeit drugs. It requires random sampling and monitoring of drug quality in pharmacies and hospitals. Furthermore, it assigns heavy penalties for offenders: Six months to life imprisonment and a huge fine of US$ 25,000. (64) The Department of Health has stepped up the drug information campaign through the use of radio and television to stop counterfeiting. (71)

In Vietnam, post-marketing surveillance activities have been undertaken by the institutes and provincial laboratories. The post-marketing quality surveillance system that uses simple testing kits developed by the National Institute of Drug Quality Control helped decrease the rate of drug failure. (13)

Cambodia adopted a social marketing program to improve the availability of quality-assured antimalarial drugs coupled with an information campaign about fake drugs. Such strategies significantly reduced the prevalence of counterfeit antimalarials in the country. (72)

Experts from the WHO gathered in Hanoi, Vietnam, November 11-13, 2003, to discuss ways of addressing the problem of counterfeit drugs (which pose a serious threat to public health) with various officials from countries in the Mekong Region. Meeting participants discussed efforts to raise awareness of the problem among policy decision makers, health care professionals, and the general public. The meeting advocates for strengthening inspection and post-marketing surveillance. (66)

## VIII.  CONCLUSIONS/RECOMMENDATIONS

Based on the information presented in studies and reports, this review concludes that the availability of poor quality drugs, especially anti-infectives, is widespread in Asia and the problem needs to be addressed. Use of these drugs endangers lives, wastes scarce resources, and contributes to drug resistance. Benjamin L. England, Regulatory Counsel to the Senior Associate Commissioner for Regulatory Affairs at the U.S. FDA, sums up the steps to tackle this problem in a statement he made before the 2002 Global Forum on Pharmaceutical Anti-Counterfeiting in Geneva: "…through the combined effects of a well designed, proactive regulatory rubric; investigative and enforcement commitments; and partnerships with stakeholders, render an environment that acts as a matrix of detection and interdiction of counterfeits, and generates evidence of counterfeiting activity earlier in the process." (18)

**At the national level**

*National drug quality assurance system*

To combat the effect of counterfeit and substandard drugs, the WHO recommends that each country develop a strategy based on its own situation — depending on their available infrastructure, and human, financial, and other resources — and include it in their overall national drug quality assurance system. It recommends that the country assess their current situation and that other concerned parties, namely government agencies, pharmaceutical industries, drug suppliers/importers/distributors, health care professionals, consumers, public interest groups, and nongovernmental and international organizations, participate in the development and implementation of a plan with clear, realistic, and attainable goals. Each party involved should have clearly defined roles to ensure accountability. Progress on the implementation of the plan should be monitored and evaluated periodically in order to

determine the successes and failures and be able to undertake corrective actions in a timely manner. (15)

*Political will, commitment, and drug regulation*

Political will and strong commitment of the government are necessary in order to make a concerted effort to improve drug quality. Comprehensive drug regulations should be enacted to include provisions prohibiting the manufacture, import, and sale of counterfeit drugs. Drug regulation covers the areas of drug evaluation and registration, marketing authorization, licensing, inspection, legislation, quality assurance, control of promotion, and advertising. (15)

*Drug regulatory authority*

Governments should strengthen or establish adequately resourced drug regulatory authorities (DRA) (15, 73) with the appropriate powers to oversee the licensing and authorization of pharmaceutical products and manufacturing sites and to conduct inspections of locally manufactured and imported medicines. They also should provide the necessary support for the proper enforcement of the drug laws and regulations. DRAs need to ensure that the manufacture, importation, distribution, supply, and sale of drugs are carried out under specific licenses/authorization in licensed/approved premises under the supervision of qualified persons. (15) Monitoring and surveillance of the premises should be conducted regularly to ensure that practices are in compliance with the specified requirement and standards. An appropriate post-marketing surveillance should be in place. The ports of entry of drugs, as well as the drug establishments (drug manufacturing industries, wholesalers, and retail pharmacies), should be regularly inspected and samples should be collected and tested for quality. (3, 15)

*Drug inspectors*

Drug inspectors should be sufficient in number and adequately trained and authorized to enter premises and seize any suspected counterfeit drugs. (3, 15, 74)

*Drug quality control laboratory*

A drug quality control laboratory with adequate equipment and trained personnel should be established. (3, 15) Those countries with less-developed laboratories could use simpler, less resource-demanding testing or screening methods for drug quality, such as TLC. These simple methods, however, do not replace the pharmacopeial, compendial, or legally accepted test methods. (15)

*Law enforcement*

There should be an effective mechanism to conduct criminal investigation and prosecution of those involved in counterfeiting, to impose appropriately severe penalties on convicted offenders, and to enforce the laws. (74, 75)

*Cooperation among stakeholders*

A closer national collaboration between the drug regulatory authority and the customs, police, professional and consumer organizations, pharmaceutical companies, distributors, and other relevant institutions is recommended. (74, 76) The governments should organize training courses for inspectors, examiners, enforcement officers (police, customs officers), health care professionals, and other relevant personnel on how to detect counterfeit drugs. (75) These governments can also undertake advocacy campaigns targeted at consumers and providers.

They are encouraged to foster international cooperation in controlling pharmaceuticals, and to enter into bilateral and multilateral agreements with other governments and with international organizations, such as the WHO, Interpol, and the World Customs Organization. (20, 74)

Importing countries should follow the following recommendations set forth by the WHO Expert Committee on Specifications for Pharmaceutical Preparations: (77)

- Establish an effective national product licensing system for pharmaceutical products;

- Incorporate the WHO "Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce" into national statutes or regulations;

- Establish a small national drug quality control laboratory as recommended by the WHO;

- Undertake samplings of products within the distribution chain as an element in quality surveillance.

(In the U.S., the law [section 321] requires, among other things, that foreign drug and device manufacturers provide the FDA certain information, including known shippers and importers of their products to the U.S., before the drugs or devices are imported. [18])

*Availability of inexpensive, quality assured drugs*

Reducing the price and increasing the availability of genuine drugs will help curb counterfeiting. A good example of this effective strategy is the social marketing campaign of quality-assured, pre-packaged drugs conducted by the government of Cambodia. It provides the patients with an easily recognizable and affordable alternative. (4, 73, 78)

In order to improve the availability of good quality drugs, Medicins Sans Frontieres suggests the following: (73)

- Make essential drugs physically available;

- Adapt prices to local revenues, or find sustainable financing mechanisms for unaffordable drugs, by means of a mix of mutually supportive strategies, such as:

  ‣ differential prices from pharmaceutical companies,

  ‣ encouraging generic competition,

  ‣ encouraging technology transfer and upgrading local manufacturers' capacities (when relevant), and

  ‣ implementing Trade-Related Aspects of Intellectual Property Rights (TRIPS) safeguards.

*Corruption*

Recommended measures to reduce corruption include: (79)

- Creating high level commissions to conduct investigations;

- Offering courses and seminars to increase awareness of the problem;

- Simplifying administrative procedures; and

- Strengthening financial management.

As a temporary measure, some countries employ expatriates who do not belong to the bureaucratic culture and have no affinity to the local population for sensitive posts. (80)

*For health care professionals*

Doctors and pharmacists should be on the alert for counterfeit/substandard drugs. Ineffectiveness of a drug should be reported to the national adverse drug reactions monitoring system and should be registered as an adverse effect. (81)

Pharmacists should purchase stocks from reputable sources (dealers who are accredited or can be trusted). They should report any suspicious drugs and withhold their sale. They should be wary of drugs offered at a price far below the current value. The UK Medicines Control Agency advises dispensing drugs in original packs. (6, 74)

Health workers at all levels should be suspicious when encountering medicines that are poorly packaged and contain no clear information about the producer. They should alert the local, national, and possibly international authorities, enabling them to conduct investigations and take the necessary actions. (74, 82)

*For consumers*

Considerable publicity (through posters, radio, television, etc.) is required to help educate consumers to differentiate the curative from the dangerous medicines. (20, 74, 78) A good example of how public education can have a major impact is the information campaign in Cambodia on how to detect counterfeit antimalarials by their external appearance, backed by dye-testing and quality assurance. (72, 78)

Consumers should be advised to: (20, 74, 81, 83, 84)
- Buy drugs from legitimate sources (pharmacies only) and not from the marketplaces, hawkers, or peddlers;
- Buy drugs in a reliable pharmacy before leaving home for holiday or business trips abroad;
- Never use drugs with deficient, damaged, or soiled packaging;
- Do not use drugs without detailed information on their exact designation, expiry date, batch number, or the name of the manufacturer, or drugs with obviously incorrect information;
- Do not use drugs if their shelf life has already expired;
- Be wary of unusually inexpensive drugs; and
- Report to their prescribers or physicians any lack of improvement in their health status in spite of the therapy or any adverse reactions experienced.

**At the international level**

At the international level, combating counterfeit and substandard drugs requires cooperation between the governments or drug regulatory authorities of drug exporting countries and between governments and international organizations such as the WHO. International surveillance should be coordinated and information should be shared not only with government drug regulatory authorities, but also with customs, police organizations, pharmaceutical companies, NGOs, health care providers, and consumers through appropriate means of communication. (13) A global mechanism should be established to curb such illegal activity.

Governments should implement appropriate laws that recognize the import, national transit, and export of counterfeit goods into, across, and out of their customs territories as a customs offense. They should grant their customs services legal powers to seize the suspected goods with the prospect of forfeiture if they are proven to be fakes. (83)

International organizations could lend support by partly subsidizing the cost of in-country testing of drugs and partly by supporting cross-checking in other countries. This helps reduce the burden on national health budgets or the consumers. (85)

**For pharmaceutical manufacturers, wholesalers, and traders**

Pharmaceutical manufacturers, wholesalers, and traders should: (83, 86)

- Be cautious in the procurement of active pharmaceutical ingredients (APIs) and finished products, and when introducing products into the distribution chain; not only should the brand be protected, but it is also necessary to identify and protect known supply chains and distribution routes; (18)

- Maintain vigilance in detecting counterfeiting or substitution of dosage forms and APIs;

- Share information with regulatory authorities, though this information should be handled with due discretion to avoid loss of confidence in legitimate products;

- Rigorously implement GMP in the manufacture of APIs;

- Manufacturers of finished dosage forms should buy APIs from the original manufacturer whenever possible or, when buying through traders, insist on transparent and full documentation concerning the origin, and demand certificates of analysis;

- Manufacturers of finished dosage forms should be aware of their responsibility and liability in assessing and ensuring the quality of the APIs and other starting materials that they use, and the rigorous conditions outlined by the WHO Expert Committee on Specifications for Pharmaceutical Preparations [Thirty-second report, WHO Technical Report Series, Number 823, WHO, Geneva, 1992];

- Wholesalers should discourage the distribution of products through a large number of intermediaries, apply Good Distribution Practice (GDP), and collaborate with regulators/ license holders. (74)

Some experts recommend that the pharmaceutical industry support governments by helping them train drug inspectors and analytical chemists, by monitoring their customers, by doing business only with accredited wholesalers, and by sharing information with the governments in order to facilitate proper legal action. (In the past, pharmaceutical companies had a tendency not to publish such problems for fear of eroding the public confidence in medicines.) Pharmaceutical companies can also help by making their genuine products affordable, thereby making fraud less profitable. (6, 87)

In addition to collaborating with regulators, the Medicines Control Agency of the United Kingdom suggests that pharmaceutical manufacturers improve their in-house security and conduct regular market surveillance. (74)

Authentication techniques such as holograms, fluorescent markers, digital watermarks, etc., can be used by pharmaceutical companies to identify their genuine products, (88) as in the case of Guilin Pharma of China, which developed a hologram to attach to the packet and blister pack of artesunate in response to the widespread counterfeiting of artesunate in Asia. (78) Manufacturers should set up appropriate security measures to detect and prevent diversion of ingredients, products, and packaging materials for illegal purposes. Regular sampling and analysis of drugs in circulation can deter counterfeit activities. (83)

## IX.   COUNTRY-SPECIFIC RECOMMENDATIONS
### (based on the information presented in the studies/reports)

**Bangladesh:** The national drug policy should be strengthened and implemented. Because people in the rural areas primarily suffer the consequences of use of substandard drugs, it is the primary care system in the rural areas that needs to be improved. The government health centers should have a steady supply of good quality medicines. Qualified physicians are needed as well as other health promoters who should make people aware of the importance of good hygiene and sanitation. International organizations are needed to help develop the rural health care system and to promote high quality and rational use of drugs. The government should exercise more vigilance in the rural areas in their efforts to eliminate substandard drugs. (35)

**Cambodia:** Although the study conducted by the Ministry of Health's Committee for Research and Study on Counterfeit Drugs showed the prevalence of counterfeit drugs was only 13.04%, it is believed that figure could be higher due to the fact that people who live in the remote areas choose to buy their medicine from small illegal drug outlets that abound throughout the country (2800 unlicensed outlets). Stricter controls should be enforced at the points of entry because counterfeit and substandard drugs are more of a cross-border problem than a local problem. (No domestically produced sample failed the test.) (41)

The Committee for Research and Study on Counterfeit Drugs made the following recommendations to the Ministry of Health and to the government of Cambodia to resolve the problem of counterfeit and substandard drugs: (41)

- Enactment of more specific regulations;
- Increased public awareness through improved education of the public;
- Increased number of qualified competent drug controllers and drug inspectors;
- Empowerment of drug inspectors;

- Closer collaboration and cooperation between regulatory agencies to combat pharmaceutical anarchy;
- Post-marketing surveillance and improvement of testing capacity; and
- Increased budget.

The government's social marketing program and the informational campaign directed at consumers have proved to be effective strategies in combating fake drugs, as reported by Seyha R at the 2002 Global Forum on Pharmaceutical Anti-Counterfeiting held in Geneva. After an information campaign about fake antimalarials, a follow-up survey conducted in August 2000 found only 25% prevalence of the fake drugs available in the market, down from 70% in 1999. (72)

**India:** A pharmaceutical business journal published an editorial suggesting that a national program consisting of the Center, state governments, NGOs, and the pharmaceutical companies be set up. This program should have sufficient regional action groups. To ease financial constraints on the part of the government, the pharmaceutical companies could help finance such a program, as their business interests are at stake. All state governments should strengthen drug control administration by employing an adequate number of inspection staff. Most state drug administrations in India do not have an adequate number of inspectors or of testing laboratories. (49)

The expert committee set up recently to examine India's regulatory system recommends a new structure for the country's drug regulatory system. Among the recommendations include setting up a National Drug Authority, suggesting measures to address the problem of counterfeit drugs, and changing the Drugs and Cosmetics Act of 1940 and the judicial procedures related to offenses committed under the Act. (70) Stiffer penalties (death, 10 years minimum prison sentence, and higher fines) will be invoked for those violating the drug laws. The committee suggested establishing a Central Drug Administration that will control the licensing of all drugs in lieu of the current licensing system whereby state drug regulatory agencies allow the manufacture of drugs which are not approved by the central regulatory agency. Other recommendations included greater surveillance, more frequent testing, and paying informers who can help track down producers of fake drugs. (50)

The Organization of Pharmaceutical Producers of India (OPPI) suggested measures such as increasing consumer awareness, appointing officers in each state's regulatory authority who would be responsible for issues concerning fake drugs, design registration, copyright litigation, inspection and control of sources of chemical supplies, imposition of heavy penalties on manufacturers of counterfeit drugs, enactment of a law similar to India's Prevention of Terrorism Act, and constant vigilance by companies. (51, 89)

**Myanmar (Burma) and Vietnam:** The findings of the WHO study on these two countries confirm that regulatory measures such as drug registration, effectively implemented, can improve the quality of drugs being sold in the market. Drug regulation needs to be well-organized and strictly enforced. (13) It is necessary to have trained staff, resources, and tools for implementation.

The manufacture, importation, exportation, distribution, and sale of counterfeit and substandard drugs should be prohibited and considered a criminal offense with violators subjected to severe penal sanctions. (13)

An effective licensing system should be maintained to ensure that the manufacture, importation, storage, supply, and sale of drugs are carried out by qualified personnel on the premises that meet the regulatory requirements. (13)

Drug registration should be strengthened to ensure that all domestic and imported products are evaluated for safety, efficacy, and quality prior to marketing. Drug regulatory authorities should have an adequate number of qualified staff to handle this task. Drug inspection in both countries should be strengthened to ensure the compliance of domestic pharmaceutical industries and distribution outlets with GMP and good distribution practices, respectively. There should be sufficient and adequately trained inspectors with authorization to enter premises and seize counterfeit/substandard drugs. (13)

The points of entry for imported drugs should be defined and stringent inspection and surveillance should be carried out jointly with customs and police to prevent smuggling. (13)

Selling drugs in marketplaces and street corners should be prohibited. The public should be educated and advised to buy their medicines from legitimate outlets only. (13)

## X.    USP EXPERT COMMITTEES REVIEW

The USP panel reviewers as well as ad hoc reviewers agreed on the recommendations set forth in this document. Additional recommendations include the following: (2, 90)

- Develop an executive summary of this review and disseminate it to the media worldwide. The summary should include a list of the countries that are not in compliance with world standards. It should also explain the dangers of adulterated anti-infective drugs and the reason why regulations and their enforcement are critical to good health and development.

- Exert international pressure on the target countries to "clean up" and enforce their quality control programs.

- The WHO, European Union, and the U.S. State Department should issue "travelers advisories" about the dangers of taking adulterated drugs in listed countries. Countries that comply with international standards can be taken off the list once compliance is assured. Such strategy was found to be highly effective in controlling the severe acute respiratory syndrome (SARS) epidemic.

- Work with the international community to develop a plan for collecting additional, high quality data on drug quality through standardized and strategic sampling to fill gaps (e.g., antiretrovirals for HIV) or monitor new initiatives (e.g., Global TB Drug Facility [GDF], Global Fund to Fight AIDS, Tuberculosis and Malaria [GFATM]) that will increase the availability of anti-infective drugs.

- Work with national and regional counterparts to set up routine monitoring of drug quality.

- One reviewer commented that efforts to improve drug quality have their own unique challenges: different languages, economic pressures (i.e., consumers buying fewer expensive drugs though they suspect the substandard quality, political connections, and corruption), illegal status of migrants, and reluctance to use drugs from the public sector. (2)

**ANNEX 1**

# VARIOUS DEFINITIONS OF COUNTERFEIT DRUG

**United Kingdom (UK)**

The Association of the British Pharmaceutical Industry (ABPI) and the Royal Pharmaceutical Society of Great Britain (RPSGB) define counterfeiting of medicine as a "deliberate and fraudulent mislabeling of medicine products with respect to identity and/or source. A counterfeit product is not made by or with the approval of the product license holder but is sold as if it were the genuine article. Counterfeit products may include products with the correct ingredients, wrong ingredients, without active ingredients, with insufficient quantity of active ingredients, or with fake packaging." (26)

The Medicines Control Agency (MCA), which is the Executive Agency of the Department of Health in the UK, has identified three different counterfeit types: (74)

- Look-alikes ─ similar packaging little or no active ingredient;

- Identical copy ─ identical (packaging and formulation); and

- Relabeled products ─ expired authentics.

**Pakistan**

The Pakistan Manual of Drug Laws defines a counterfeit drug as "a drug, the label or outer packing of which is an imitation of, resembles or so resembles as to be calculated to deceive the label or outer packing of a drug manufacturer." (91)

**Philippines**

The Republic Act No. 8203 defines a counterfeit drug to mean "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:

- 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 (BPTTT) in the name of another natural or juridical person;

- A drug product refilled in containers by unauthorized persons if the legitimate labels or marks are used;

- An unregistered imported drug product, except drugs brought in the country for personal use as confirmed and justified by accompanying medical records, and

- A drug which contains no amount of or, a different active ingredient, or less than eighty per cent (80%) of the active ingredient it purports to possess, as distinguished from an adulterated drug including reduction or loss of efficacy due to expiration." (92)

**China**

Chinese criminal law (Articles 140 and 141 of the Chinese Criminal Code) applies in cases of the manufacture and sale of counterfeit pharmaceuticals whenever:

- The pharmaceutical product contains none of the active ingredient.

- The pharmaceutical product is deemed to be harmful to human health.

- The counterfeit medicine will negatively affect the health of the patient.

- The medicine will severely impact or limit the patient's recovery.

Criminal liability in China for trademark counterfeiting applies in cases where the counterfeit drug contains some of the active ingredient of the genuine product and is not considered to be harmful to human health. (27)

**ANNEX 2**

# ASSESSMENT OF DRUG QUALITY

## Determinants of drug quality

According to the *USP Drug Quality and Information (DQI) Training Manual on Good Laboratory Practices, Basic Tests, and Sampling Procedures*, the final drug quality of a manufactured product is determined by: (32)

- Raw/starting ingredient(s)

- Plant environment

- Formulation

- Manufacturing process and equipment

- Technical know-how for producing and packaging it

- Transportation

- Storage conditions.

## Quality control tests for drug products

The analytical procedures to control the quality of a final market drug product should include both qualitative and quantitative methods in order to assure its identity and purity.

The different categories of tests include: (31)

- Identification test — to confirm the identity of the principal component of a lot of raw material or formulation, e.g., color tests, melting points of the drug or its derivative.

- Quantitative analysis of the drug substance — to determine the percent purity of the drug substance or the content of the active ingredient(s) in formulation. There are two types of tests:

  ‣ Absolute methods, e.g., titrations, gravimetric procedures; and

  ‣ Relative methods, e.g., gas chromatography (GC), high pressure liquid chromatography (HPLC), spectrophotometry (ultraviolet, visible or infrared).

- Tests for specific impurities — to control the quantity of a specific impurity or group of impurities in the drug product, such as water solvents, metals, and trace organic impurities. The tests used for quantitative analysis of the drug substance can also be used to test for impurities. Other tests include semi-quantitative limit tests using relative size of spots on thin layer chromatograms and spot tests with visual color comparison.

- Chromatographic screen — to qualitatively examine the product for impurities, including contaminants not previously encountered, e.g., paper, thin layer, gas or high pressure liquid chromatography, electrophoresis.

- Miscellaneous tests — to control specific properties known to affect performance or required by regulatory agencies, e.g., crystal form (X-ray or infrared spectroscopy), sterility, and pyrogens.

**Quality control using basic tests**

As stated in the *USP DQI Training Manual on Good Laboratory Practices, Basic Tests, and Sampling Procedures*, basic tests are considered the minimum tests that the drug wholesaler or National Program warehouse can perform. These include the following: (32)

- Visual inspection (for dosage forms: packaging materials, coloration, shapes);

- Simple test for disintegration of tablets or capsules for preliminary assessment of deficiencies related to solubility and availability;

- Identity test using simplified color reactions for a quick check of active substance;

- Thin layer chromatography (TLC) assays for a quick check of (semi-) quantities of drug present (with 10% accuracy in most cases), thus ensuring the drug's potency.

*Quality control using pharmacopeial methods*

As stated in the *USP DQI Training Manual on Good Laboratory Practices, Basic Tests, and Sampling Procedures*, these tests can be conducted by national laboratory centers and usually involve: (32)

- Visual inspection (for dosage forms: packaging, coloration, shapes and labeling)

- Uniformity of dosage units

- Identification for active pharmaceutical ingredient (API)

- Sterility

- Dissolution

- Assay for the content of APIs.

**Basic tests**

Simple basic tests can play a very important role in detecting substandard and counterfeit drugs at a very low cost and with minimal training. They can be performed by persons other than fully qualified pharmacists or chemists and need not be carried out in a laboratory setting. While basic tests have a clearly defined and limited role in screening the identity and content of drugs, they cannot, under any circumstances, replace the requirements of pharmacopeial monographs – the only means to assure the quality of pharmaceuticals. (32)

*Visual inspection*

Visual inspection can identify missing or incorrect accompanying documents, defective dosage forms, packaging with incomplete, damaged or missing labels, or labels written in a foreign language. Drug products found with such discrepancies or inconsistencies should be subjected to further tests (disintegration, identity tests). (32)

*Disintegration test*

Disintegration is defined as the state in which no residue of the tablets and capsules, except fragments of undissolved coating, remains in the test solution. Tablets should be sufficiently hard to withstand handling without crumbling or breaking but they should also be sufficiently soft for easy disintegration in the stomach or intestine in order to make the drug available to the body. Tablets and capsules may harden and fail the disintegration test because of poor drug processing or incorrect storage. A simplified disintegration test determines whether or not tablets or capsules will dissolve in water within 30 minutes at 37± 2 °C. (32)

Counterfeit drugs, such as capsules containing sand or ground ceramics or tablets consisting of flour, can easily be detected by disintegration tests. Ground or sand ceramics settle to the bottom of the flask while the supernatant liquid remains clear or almost clear. Preparations containing flour never truly disintegrate but absorb water and form a sticky mass or disintegrate in a couple of sticky lumps slowly settling at the bottom of the container. High quality tablets and capsules containing modern disintegrants react differently, for example, uncoated tablets of good quality will normally dissolve completely in water at 37 °C within 15 minutes. (32)

*Thin Layer Chromatography*

TLC is a method used for separating chemical compounds based on polarity. (93, 94) It involves the separation of individual components of a sample using a thin layer prepared from a suitable stationary phase by developing the test target substance with a suitable mobile phase.

Uses of TLC
- TLC can be used to obtain a qualitative analysis to determine the presence of a particular substance in a mixture. An estimate of the substance level may also be performed.

- TLC can be used as a quantitative analysis to determine the amount of a particular sample in a sample mix. Accurate estimates of quantity can be measured by comparison.

- TLC can be used as a preparative analysis to purify and isolate a particular substance by separating it from any contaminants. The components remain in the adsorbent and can be retrieved for further experimentation. (32)

Advantages of TLC
- TLC allows the simultaneous analysis of many samples at the same time under the same conditions as opposed to HPLC, which requires sequential analysis.

- TLC can be used to make presumptive identifications.

- TLC uses a fresh adsorbent for each analysis, which eliminates the problems of adsorbent contamination from previous analyses and worn columns as observed in HPLC. The amount of solvent needed for TLC is much less than with HPLC.

- TLC does not require complex instrumentation or the associated maintenance costs.

- TLC methods are portable and can be performed outside of the laboratory.

- TLC can be used for rapid screening of pharmaceuticals in places such as ports of entry, distribution centers, or areas lacking resources for other more costly analyses.

- TLC has great flexibility in terms of stationary and mobile phases.

- TLC use has no detection problems in the case of non-elution, thermal instability, and masking by solvent, as is the case with HPLC or GC, because the applied substance remains on the plate. (32)

Used as the primary screening method, TLC can be cost effective. It may not provide definitive answers on drug quality but it can limit the number of drugs that would require confirmatory analysis. (53)

*U.S. FDA TLC Kit*

In the early 1990s, the U.S. FDA developed a TLC kit that costs about $100.00 and can be used for hundreds of test runs. It provides rapid qualitative and semi-quantitative (85 to 115% of stated content) screening of drug content. It does require electricity but needs only minimal training to perform the procedure. (93) The TLC kit is lightweight, portable, and unbreakable and has demonstrated 98% sensitivity and specificity. It has been recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations as a primary independent screening method. It has been successfully used in detecting diethylene glycol contamination of glycerin in Haiti (24, 95), and in Swaziland's first drug quality screening laboratory (96) as well as in the screening of the quality of fixed-dose combination (FDC) drugs for tuberculosis. (5)

*GPHF-Minilab*

TLC is one of the analytical techniques employed in the testing of drug quality using the GPHF-Minilab, a mini-laboratory kit recently developed by the German Pharma Health Fund (GPHF). The Minilab was designed specifically for developing countries as a rapid screening method to detect counterfeit and substandard drugs. It is described as a complete laboratory assembled in two cases and provides a set of starter-kit chemicals for performing basic drug quality control at a very low cost. A kit costs about US$ 3,422. The start-up package includes reagents and solvents that allow 3000 identity checks by color reactions and 1000 content checks by TLC. (97)

Minilab drug quality testing consists of four stages: (97)

- Visual inspection of the product, packaging, and labeling for rapid rejection of the more crudely presented counterfeits,

- Simple tablet and capsule disintegration test performed in lukewarm water, a preliminary assessment of deficiencies related to drug release; drugs that are badly manufactured or poorly stored often fail this test;

- Simplified color reactions for a quick check of any drug present, thereby ensuring that the drug is actually present;

- Thin layer chromatographic run for a quick check to find out whether the quantities of drug claimed on the label are actually in the product.

Samples found to be potentially counterfeit or substandard would require further testing according to legally accepted reference method(s) for confirmation purposes. (97)

The use of the Minilab helps to reduce the workload of central drug control laboratories as well as to keep the cost of drug analysis within the national health budgets of developing countries. (97)

## Other testing methods

High technology analytical methods such as mass spectrophotometry are also used, especially for pharmaceuticals that are considered "sophisticated counterfeits." However, they are considered expensive for developing countries to use. (15) HPLC is an analytical method used in the assessment of content in pure and formulated drugs and in the determination of exogenous compounds in biological matrices. HPLC has the ability to separate the parent drug from related compounds. It determines the amount of active ingredient as well as impurities in any formulated pharmaceutical products. (67)

Green MD et al of the U.S. Centers for Disease Control and Prevention (CDC) developed and validated a simple colorimetric field test (ARTS-Fast Red TR [FRTR]) to identify fake artesunate tablets. This assay was modified to identify the presence of artemether as well as dihydroartemisinin. This method can be used for quick visual assessment of tablet authenticity. It can also quantify the drug content of the tablet when used in combination with a spectrophotometer. (98)

Furthermore, Green and his colleagues developed a simple test using a hand-held refractometer, a "low tech" device that measures the specific gravity of urine samples and costs less than US$ 100. The amount of active ingredient in a certain tablet can be determined by measuring the specific gravity. Once the drug dissolves, a drop of the solution is placed in the refractometer, which gives the refractive index, which in turn is converted to a specific gravity and compared with a standard already established for that particular drug. (99)

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