COUNTERFEIT

DRUGS

Guidelines for the development of measures to combat counterfeit drugs

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Other Medicines
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This document has been prepared under the auspices of the DMP-DAP Joint Project on Counterfeit Drugs which was administered by the World Health Organization Division of Drug Management and Policies (DMP) and the Action Programme on Essential Drugs (DAP) from 1995 to 1997. With effect from January 1999, the Department of Essential Drugs and Other Medicines Department (EDM) includes the former DAP and most components of DMP.

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Executive Summary

In 1988, the World Health Assembly adopted resolution WHA 41.16, which requested the Director-General of WHO to initiate programmes for the prevention and detection of the export, import and smuggling of, *inter alia*, counterfeit pharmaceutical products. This resolution was reinforced by another WHA resolution in 1994, WHA 47.13, which asked the Director-General to assist Member States in their efforts to ensure that available drugs are good quality, and in combating the use of counterfeit drugs.

These guidelines respond to the WHA requests: They are aimed to provide guidance to Member States in developing their own national measures to combat counterfeiting of drugs.

The guidelines provide an overview of the problem and factors contributing to the counterfeiting of drugs. They outline also the steps to be followed in developing national strategies as well the specific measures to be considered in combating counterfeit drugs. Issues such as, approaches to country studies, inspection of suspected counterfeit drugs, screening of potentially counterfeit products and training of human resources are also dealt with in the guidelines.

The problem

Information on the scale of the problem is inadequate and there are no global studies conducted. However, it is known to affect both developed and developing countries. The problem is more pronounced in countries where the manufacture, importation, distribution, supply and sale of drugs are less regulated and enforcement is weak.

So far, the counterfeit drugs that have been discovered have rarely been efficacious and, in many cases have been positively dangerous and detrimental to public health.

The factors facilitating the occurrence of counterfeit drugs vary from country to country. However, the most common factors are considered to be: lack of legislation prohibiting counterfeiting of drugs; weak penal sanctions; weak or absent national drug regulatory authorities; weak enforcement of drug laws; shortage/erratic supply of drugs; lack of control of drugs for export; trade involving several intermediaries and free trade zones; and corruption and conflict of interest.

National strategies

There is no simple or standard solution that is applicable to all countries to eliminate the problem. Each country has to develop a strategy based on its own situation taking into account the available infrastructure and human and other resources. This should be part of the overall national drug quality assurance system.

In developing a national strategy, assessment of the current situation should be the starting point. All concerned parties: government agencies, pharmaceutical industries, drug suppliers, health care providers and professionals, consumers, nongovernmental and international organisations should be involved in the process of development and implementation of the plan. The plan should have clear and realistic goals that are attainable. The role of each party must be clearly defined to ensure accountability. Progress on implementations of the plan of action should be monitored and evaluated from time to time to identify successes or failures and take timely corrective actions.

Specific measures

Political will

At national level, political will and strong commitment of the government are critical if there is to be a concerted effort to improve drug control and decrease the prevalence of counterfeit drugs. Governments have to enact comprehensive drug legislation, including provisions prohibiting the manufacture, import and sale of counterfeit drugs.

Establishing drug regulatory authorities

Governments have to establish adequately resourced drug regulatory authorities (DRA) with the appropriate powers. Governments should provide the necessary support to ensure the enforcement of the drug laws and regulations.

Drug regulatory authorities need to ensure that the manufacture, importation, distribution, supply and sale of drugs are carried out under specific licences/authorisation in licensed/approved premises under the supervision of qualified persons. They should conduct regular monitoring and surveillance of premises to ensure that practices employed in the manufacture, import, distribution and sale of drugs comply with the specified requirements and standards. They should ensure that all drugs in the national drug distribution channels have been authorised/licensed. The ports of entry and drug establishments, including drug-manufacturing industries, wholesalers and retail pharmacies must be regularly inspected and samples collected and tested.

DRA inspectors play a crucial role in the identification and investigation of counterfeit drugs and in the prosecution of counterfeiters. There should be sufficient and adequately trained drug inspectors with authorisation to enter premises and seize any drugs suspected of being counterfeit. Countries that do not have full-fledged drug quality control laboratories should look for simpler and less resource demanding testing/screening methods for the identification of counterfeit drugs. Thin-layer chromatography, test-tube colour reactions, melting point determination could be considered to serve the purpose. However, such simple tests or screening methods must not be considered as a replacement of pharmacopoeal, compendial or legally accepted test methods. Products considered to be potentially counterfeit have to be subjected to further testing according to the pharmacopoeal, compendial or legally accepted reference method(s).

A shared responsibility

Combating counterfeiting of pharmaceutical products at national level is a shared responsibility involving, relevant government agencies, pharmaceutical manufacturers, distributors, health professionals, consumers and the general public. Governments have to create the appropriate environment for the participation of all concerned partners. Similarly, cooperation and collaboration between the various government agencies such as the DRA, customs, police, is also essential for any success in this field.

Counterfeiting of pharmaceuticals is of international dimension. There is therefore, a need to foster intercountry, subregional and regional cooperation in the fight against the counterfeiting of drugs.

1. Introduction

These guidelines for developing measures to combat counterfeit drugs have been prepared within the framework of the World Health Organization (WHO) DMP-DAP Joint Project on Counterfeit Drugs which ran from 1995 to 1997 (see section 1.2). Their purpose is to assist Member States of WHO in efforts to prevent the infiltration of national drug distribution channels by counterfeit drugs. The guidelines are aimed principally at governments, national drug regulatory authorities, national law enforcement agencies and the judiciary. It is hoped that they will also prove useful to the pharmaceutical industry, drug importers, distributors, relevant professional associations and consumers.

1.1 Background

Concern about the quality of drugs is as old as drugs themselves. Writings from as early as the fourth century BC warn of the dangers of adulterated drugs and, in the first century AD, the Greek physician Dioscorides identified such products and advised on their detection. Despite all the advances made over the years, this concern has not disappeared. In the recent past, the unregulated proliferation of pharmaceutical industries and products has brought with it many diverse problems of varying magnitude. Counterfeiting is just one example.

Concern regarding the quality of drugs in international commerce took on a global dimension following the establishment of WHO in 1948. In 1951, WHO Executive Board adopted resolution EB7.R79, which requested the Director-General to consider the advantages of more uniform methods for the control of drugs in countries in the interest of health and international commerce (*1*).

The problem of counterfeit medicines was first addressed at the international level in 1985 at the Conference of Experts on the Rational Use of Drugs in Nairobi. The meeting recommended that WHO, together with other international and nongovernmental organizations, should study the feasibility of setting up a clearing house to collect data and to inform governments about the nature and extent of counterfeiting (*2*).

In 1988, the World Health Assembly adopted resolution WHA41.16 which requested the Director-General of WHO to initiate programmes for the prevention and detection of the export, import and smuggling of falsely labelled, counterfeited or substandard pharmaceutical preparations. The resolution also requested the Director-General to cooperate with the Secretary General of the United Nations in cases when the provisions of the international drug treaties are violated (*3*).

The first international meeting on counterfeit drugs, a workshop organized jointly by WHO and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), was held from 1 to 3 April 1992 in Geneva in response to this resolution (*4*). The participants agreed on the following definition:

A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging.

The workshop also adopted comprehensive recommendations which urged the commitment of all parties involved in drug manufacture, distribution and use, including pharmacists and consumers, in solving the problem of counterfeit drugs.

Given the rapid spread of counterfeit drugs in many national drug distribution channels, the World Health Assembly in 1994 adopted resolution WHA47.13. This requested the Director-General of WHO to assist Member States in their efforts to ensure that available drugs are of good quality, and in combating the use of counterfeit drugs (*5*).

1.2 DMP-DAP Joint Project on Counterfeit Drugs

In 1995, in pursuance of resolution WHA47.13, WHO, with financial assistance from the Government of Japan, launched the DMP-DAP Joint Project on Counterfeit Drugs, to be administered jointly by its Division of Drug Management and Policies and Action Programme on Essential Drugs. The objective was to assist Member States in the assessment of the problem of counterfeit drugs and in the development of measures to combat counterfeiting.

The present guidelines are one of the outputs of the Project, and were developed through a series of consultations (see Box 1).

Box 1
Consultations held to develop the guidelines on counterfeit drugs

- *Assessment of the scale and problems of counterfeit drugs* (11–13 September 1995)
  This meeting developed a protocol for the collection of information on the pharmaceutical sector at national level. Special emphasis was placed on drug regulatory activities, and those elements of drug supply and quality assurance systems that have relevance to the assessment of the scale and problems of counterfeit medicines (*6*).

- *Use of simple test methods to detect counterfeit pharmaceutical products* (14–15 September 1995)
  Approaches to the detection of counterfeit drugs and simple tests for pharmaceutical products suspected of being counterfeit were discussed (*7*).

Box 1. Consultations held to develop the guidelines on counterfeit drugs
(continued)

- *Simple test methods and inspection aimed at the detection of counterfeit pharmaceutical products* (6–10 November 1995)
  This consultation focused on specific issues of inspection relating to counterfeited and substandard pharmaceutical products in distribution channels. Consultants reviewed provisional guidelines for inspection of drug distribution channels from the viewpoint of detecting counterfeit medicines (*8*).

- *Education and training of drug inspectors and drug analysts involved in the detection and eradication of counterfeit drugs* (28–30 August 1996)
  The objectives of this consultation were: (1) to provide appropriate guidance to the organizers of programmes to be used in education and training for the inspection and examination of counterfeit medicines; and (2) to provide help to national authorities in implementing such programmes (*9*).

- *National implementation guidelines for combating counterfeit drugs* (30 October–1 November 1996)
  This meeting formulated recommendations to governments of Member States on how to develop a programme for combating counterfeit medicines (*10*).

- *Progress and planning of the counterfeit drugs project* (24–26 March 1997)
  This consultation reviewed the progress of the Project and advised WHO on future actions (*11*).

- *International workshop on counterfeit drugs* (26–28 November 1997)
  The conclusions of the above consultations were consolidated into a draft manual on combating counterfeit drugs which formed the basis of the present guidelines. The workshop made comprehensive recommendations for action at the international and national levels (*12*).

The DMP-DAP Joint Project on Counterfeit Drugs also implemented the following:

- implementation of two country studies, in Myanmar and Viet Nam (*13*)
- establishment of a network of anticounterfeit pharmaceuticals liaison officers
- improvement of the WHO database on counterfeit drugs (Circulation of the database is restricted, since the data is not validated.)
- workshop for decision-makers in drug regulatory affairs and customs officials on combating counterfeit drugs (3–5 November 1997, Hanoi, Viet Nam) (*14*)
- model training courses for senior pharmaceutical inspectors on counterfeit drugs

(7–11 November 1997, Tokyo, Japan) (*15*) and for examiners on screening counterfeit drugs (20–30 July 1998, Bangkok, Thailand).

In addition, the Project was highly successful in its advocacy to raise awareness of the problems of counterfeit pharmaceuticals. Since it ended, further international workshops on the subject have been held: Intercountry Meeting on Monitoring, Detection and Control of Counterfeit Drugs (29–30 October 1998, Manila, Philippines); and Inspection of Drug Distribution Channels (16–20 November 1998, Kampala, Uganda).

The termination of the Project does not mean completion of the work but rather the beginning of further work. The fight against counterfeit drugs must be continued, strengthened by the shared responsibilities of the parties concerned – Member States, United Nations and nongovernmental organizations, the pharmaceutical industry, health professionals and consumers.

1.3 Structure of the guidelines

For the purposes of this document, the terms **drug**, **medicine**, **pharmaceutical product** and **pharmaceutical** are used interchangeably to refer to medicinal products intended for prophylactic, diagnostic or therapeutic use.

Following this introduction, sections 2 and 3 provide an overview of the problems of counterfeit drugs and their impact on public health. Section 4 outlines the factors that facilitate counterfeiting. Sections 5 and 6 constitute the major elements of the guidelines and set out proposed strategies, approaches and measures to be taken by governments and other sectors in order to detect and prevent counterfeiting. Sections 7–10 provide supplementary guidance on the specific measures mentioned in sections 5 and 6. They cover assessment of the counterfeit problem at the national level, inspection in drug distribution channels when pharmaceutical products are suspected to be counterfeit, test methods, and appropriate training programmes. In addition to the list of references, suggestions are made for further reading, and a glossary of terms used is also provided.

2. Overview of the Problem

Counterfeiting of commercial products is an age-old practice which flourishes in many countries and is motivated mainly by the huge profits to be made. Trade in counterfeit drugs appears to be widespread internationally and affects both developing and developed countries. Over the last decade or so, it has been brought to the attention of governments and the public as never before. The spread of counterfeit drugs is generally more pronounced in those countries where the manufacture, importation, distribution, supply and sale of drugs are less regulated and enforcement may be weak. Current information indicates that drug counterfeiting is becoming more and more sophisticated, and thus the responsible authorities in Member States are advised to keep this issue under constant review.

Counterfeit drugs are not necessarily of the quality they purport to be and may be mislabelled with respect to identity and/or source. They can be imported, smuggled or manufactured locally by large consortia in large factories and establishments equipped with the most modern equipment, or by small-time operators in smaller, often poorly equipped facilities. Some examples of types of counterfeit drugs include:

- products which do not contain any of the specified active ingredients despite such declarations on the labels
- products which contain active ingredients other than those specified on their labels
- products which contain the correct strength of the specified active ingredients but whose source is different to the one declared
- products which contain the specified active ingredients but in strengths different to those declared; they may also contain different or different quantities of impurities.

National drug distribution channels have been established by law in a number of countries to ensure that the nation's drugs are of the correct quality, efficacy and safety. Unfortunately, these channels are sometimes undermined and infiltrated so that counterfeit products have been found alongside genuine drugs in legitimate channels, as well as in the illegitimate markets that exist in many developing countries. In every case, there is fraudulent intent to deliberately and knowingly manufacture, distribute, supply or sell these products for unlawful gain.

New global trade arrangements, free trade agreements and deregulation measures are dramatically changing the pharmaceutical market worldwide; they are also resulting in a proliferation of pharmaceutical products. This may set a scene which favours an increase in counterfeiting activities. Factors such as inequitable income and wealth distribution, and variable social and economic development also contribute to the increasing incidence of counterfeit.

The precise extent of the occurrence and distribution of counterfeit drugs is unknown, even though estimates derived from country studies are widely cited. Since 1982, WHO has been collecting data on counterfeit drugs. The majority of cases involved tablet and capsule dosage forms. However, there is a shortage of validated information and thus the acquisition of accurate data is a priority.

Awareness of the harmful effects of counterfeit drugs is growing in all sectors at national and international levels. Yet greater cooperation and collaboration are required between governments and relevant organizations if there is to be significant progress in the fight against counterfeit drugs.

3. Impact on Public Health

In most cases, counterfeit drugs are not equivalent in quality, safety and efficacy to their genuine counterparts. Even if they are of the correct quality or contain the correct amount of active substance, their production and distribution are not within the purview of the drug regulatory authority (DRA) of the country concerned. This means that any associated defects and adverse reactions will not be easily recognized or monitored and, if needed, an effective product recall would not be possible.

So far the counterfeit drugs which have been discovered have rarely been efficacious. In many cases, they have been positively dangerous and detrimental to public health in terms of human suffering and burden on the health services. Patients may not respond as quickly as they should and, in some instances, may not respond at all. Treatment with ineffective counterfeit drugs such as antibiotics or vaccines may have a deleterious effect on a wide section of the population. In extreme cases, counterfeit drugs may cause serious harm to health or exacerbate the conditions being treated because of the harmful ingredients they may contain. For example, the incorporation of diethylene glycol in pharmaceutical preparations, fraudulently or by mistake, has caused the death of more than 500 people, mostly children. When ingested, diethylene glycol can affect the central nervous system, liver and kidneys, and can lead to death through kidney failure. In another case, it is alleged that placebo tablets containing no active ingredients were stolen and sold as a contraceptive drug, leading, it is claimed, to unexpected pregnancy.

As a consequence of such damaging effects, counterfeit drugs may erode public confidence in health care systems, health care professionals, the suppliers and sellers of genuine drugs, the pharmaceutical industry and national DRAs. Incorrect labelling as to source can also be detrimental to the reputation and financial standing of the original and/or current manufacturer whose name is being fraudulently used.

4. Factors facilitating Counterfeiting

A variety of factors contribute to the proliferation of counterfeit drugs. These should be accurately identified, to enable governments to detect counterfeiting problems and introduce effective programmes to eradicate counterfeit drugs in national drug distribution channels. Several possible factors are considered below.

Lack of legislation

Countries need appropriate legislation in place to help in the eradication of counterfeiting. When there is little or no legislation covering the proper control of manufacturing and distribution of drugs, counterfeiting can escape prosecution.

Absent or weak national drug regulatory authority

A competent national DRA is essential if the quality of locally manufactured and imported drugs is to be adequately assessed and local manufacturing facilities properly inspected. Inadequate, ineffective or weak regulatory control could promote unregulated importation, manufacture and distribution of drugs, leading to the proliferation of counterfeit drugs in national drug distribution channels. It could also encourage the emergence of illicit markets and hence the further promotion and marketing of counterfeit drugs. Inadequate human and financial resources for drug control activities could also result in the inability of the national DRA to probe the existence of counterfeit drugs in national drug distribution channels.

Specific factors which may encourage counterfeiting activities include:

- Absence of:
  - legal mandate for
    (*a*) the licensing/authorization of manufactured drugs
    (*b*) the licensing/authorization of imported drugs
  - legal mandate for inspection
  - licensing system to regulate the production of bulk active ingredients and finished dosage forms
  - licensing system to regulate the importation of active pharmaceutical ingredients and finished dosage forms
  - licensing system to regulate the distribution and sale of drugs
  - formal procedures for the licensing/authorization of drugs
  - suitable analytical laboratory facility
- Non use of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (*16*) as a prerequisite for the authorization/import of drugs.
- Distribution of products through unlicensed/unauthorized intermediaries
- Sales of products through unlicensed/unauthorized outlets.

Lack of enforcement of existing legislation

When existing laws are not rigorously enforced, crimes such as counterfeiting tend to be perpetrated, since there is little fear of arrest and prosecution. Moreover, disregard of trademark rights may encourage large-scale counterfeiting of drugs.

Weak penal sanctions

Absence of or lenient penal sanctions for violations of drugs legislation may encourage counterfeiting.

Corruption and conflicts of interest

Corruption and conflicts of interest may adversely affect the efficiency of DRA and law enforcement personnel, resulting in a failure to arrest, prosecute and convict those responsible for counterfeiting.

Transactions involving many intermediaries

When products pass through many intermediaries or paper transactions, the opportunities for intervention by counterfeiters are increased, especially where controls are lax.

Demand exceeding supply

When demand for drugs outstrips supply, counterfeiting may be encouraged as large profits can be made from the manufacture and distribution of counterfeit products. In some cases, high demand can be generated through the inappropriate use of drugs by consumers. For example, the misuse of steroid-containing creams for bleaching the skin and of steroids for body-building have generated a large international market for counterfeited steroid-containing drugs. These are often distributed through unauthorized channels and/or illicit markets.

High prices

When drug prices are high and significant price differentials exist there is a greater incentive to supply cheaper counterfeit drugs.

Sophistication in clandestine drug manufacture

The advent of sophisticated equipment for the manufacture and packaging of drugs has increased the difficulty of detecting counterfeit products because counterfeiters can now imitate genuine drugs almost perfectly.

Inefficient cooperation between stakeholders

When intersectoral cooperation between national DRAs, police and customs services and the judiciary in combating the counterfeiting of drugs is ineffective, counterfeiters can escape detection, arrest and penal sanctions. The tasks and responsibilities of each sector should be clearly described. The reluctance of the pharmaceutical industry, wholesalers and retailers to report drug counterfeiting to the national DRA could impede the national authorities from successfully taking measures against counterfeiting.

Lack of regulation by exporting countries and within free trade zones

Pharmaceuticals made for export are not regulated by exporting countries to the same standards as those produced for domestic use. In addition, pharmaceuticals are sometimes exported through free trade zones where drug control is lax and where repackaging and relabelling take place; this can facilitate trade in counterfeit goods.

5. Developing National Strategies

5.1 General considerations

Counterfeiting of drugs is often undertaken by people and organizations involved in other types of crime, frequently on a large national or even international scale. Measures are needed to prevent the manufacture, supply and distribution of counterfeit drugs. Close cooperation between the various drug control and law enforcement agencies within countries and at the international level is required to ensure that these measures are implemented effectively.

Governments and national DRAs are the organizations with the collective prime responsibility to develop such measures. Legitimate pharmaceutical manufacturers also have a responsibility in the fight against counterfeiting. However, counter-measures are often most effective when they are instituted collaboratively by government and industry.

Experience gained so far has shown that the nature and extent of counterfeiting and the factors facilitating it vary from country to country, and that there is no single or simple way to eliminate the problem. Thus each country has to develop a strategy based on its own situation, taking into account the magnitude of the problem and the available infrastructure, and human and other resources. Even countries with a highly evolved drug regulatory system may not find it easy to design and implement appropriate strategies. Countries with less developed drug regulatory systems and accompanying shortages of trained human resources and funds may have difficulties. It is hoped such countries can be given support and guidance from international organizations, such as WHO, and from selected developed countries with experience in this area.

In the first instance, measures should be directed towards the effective detection of counterfeit drugs in national drug distribution channels, and to preventing them entering these channels. While this may not totally eradicate counterfeit drugs, it should substantially reduce the exposure of the population to the risks associated with these products. Although counterfeit drugs are known to exist in the national drug distribution channels of many countries, their extent and nature are not fully known. An assessment of the current situation is therefore the first step, ensuring that a clear distinction is made between substandard and counterfeit products. Measures should also include procedures to improve drug control systems and cooperation in enforcing existing legislation.

5.2 Plan of action

Each country should evolve a comprehensive plan of action for combating counterfeit drugs. The plan should be pragmatic and have realistic goals that are attainable with the available human and financial resources. It should embrace all those concerned: government and its agencies, the pharmaceutical industry, drug importers and distributors, health professionals and their associations, consumers, and supportive international, regional and nongovernmental organizations. The plan should include the factors in box 2.

Box 2. Plan of action for combating counterfeit drugs

- an assessment of the nature and extent of counterfeit drugs (see section 7)
- steps to improve the effectiveness of the national DRA, including the development of adequate human resources to enable it to meet its responsibilities
- an examination of existing drug control laws for their adequacy in preventing the appearance of counterfeit drugs in the national drug distribution channels; if the laws are adequate then the causes of the existence of counterfeit drugs should be investigated further; if they are inadequate they should be revised to include provisions that would assist in the detection and eradication of counterfeit drugs
- procedures for the timely enactment of appropriate laws against counterfeit drugs which would provide for the imposition of severe penal sanctions, and the allocation of adequate resources for their enforcement
- steps to ensure the adequate enforcement of drug control laws, with timely processing of all offences related to counterfeiting of drugs and appropriate sentencing of convicted offenders
- measures to foster cooperation and collaboration at national, subregional, regional, and international levels.

5.3 Monitoring and evaluation

The national DRA should monitor progress in implementing all aspects of the plan of action. Factors contributing to successes or failures should be identified. To this end suitable indicators should be developed, which could include the following:

- the specific mention of counterfeit drugs in legislation and the development of specific regulations in this area
- the authorization of drug enforcement officers to enter premises and to examine commercial documents relating to suspected supply of counterfeits, in the company of police officers, if necessary
- the availability of adequate laboratory facilities for the identification of counterfeit drugs
- a requirement for WHO-type certificates for imported drugs
- the compulsory reporting to the relevant authorities of any incidents in which counterfeits are detected or involved
- the existence of a structured system of regular meetings between the authorities, the relevant professions and the industry to review progress in implementation of the plan of action.

Measures should be designed in such a way as to promote collaboration between all parties concerned, and roles and responsibilities should be clearly defined. The specific measures required in developing and implementing the plan of action are considered in the next section.

The plan of action should be periodically evaluated and reformulated. This is particularly important in situations where it was not possible initially to implement the plan in full successfully, or where implementation has not succeeded in reducing the extent of counterfeit drugs in the national drug distribution channels. Any reformulation should take into account the results, both positive and negative, of earlier implementation steps.

6. Specific Measures

6.1 Strengthening political will and commitment

Political will and the strong commitment of the government are essential if there is to be a concerted effort to improve drug control and decrease the incidence of counterfeiting. Government responsibilities include:

- enactment/revision of appropriate legislation (see section 6.2)
- establishment of adequately resourced drug control institutions (preferably a single national DRA) with appropriate powers enshrined in legislation (see section 6.3)
- provision of adequate initial and in-service training for drug control, customs and law enforcement personnel; customs officials will require skills related to the inspection of documents accompanying any imported drugs, including export and import authorization for narcotic drugs and psychotropic substances (*17–19*), and in the identification of counterfeit drugs to enable their interception and detention at the ports of entry for detailed investigation and examination, with the assistance of qualified persons when necessary (see section 10)
- establishment of specific import procedures; this may include designation of ports of entry for imported drugs, a measure which is particularly desirable in countries with limited human resources (*20*)
- fostering international cooperation in the control of pharmaceuticals and entering into bilateral and multilateral agreements with other governments and with international organizations such as WHO and the International Criminal Police Organization/Interpol

6.2 Promulgating appropriate legislation

Legislation should be regularly scrutinized and amended as required. It should regulate the manufacture, importation, distribution, supply and sale of drugs, thereby ensuring the following.

- Counterfeit drugs are prohibited by law.
- The national DRA is specified in law and, where possible, is designated as the only agency entrusted with the responsibility of drug control. The agency should either be appropriately located within the Ministry of Health or be under its purview or jurisdiction. The powers and duties of the national DRA should also be appropriately defined by law.
- The manufacture, importation, distribution, supply and sale of drugs are carried out under specific licences/authorizations in licensed/authorized premises under the supervision of suitably qualified persons.
- All drugs in the national drug distribution channels are licensed/authorized.

- Licences/authorizations are revoked for poor or illegal performance as judged against existing laws. Renewal is required at specified intervals, and is dependent on satisfactory compliance with existing laws and regulations.
- Drugs are suitably labelled and packaged according to the specifications and claims for quality, standard, composition, safety and efficacy.
- The conditions for importation of drugs are clearly specified and importation is undertaken only with the necessary import licences/authorizations issued by the national DRA. Imported drugs are licensed/authorized in the country of manufacture or, where not, there are adequate reasons for such nonauthorization which are acceptable to the national DRA. Imported drugs are supported by the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce.
- Imported drugs are inspected at ports of entry and samples are collected and analysed as required. (Some authorities routinely sample and test all imported drugs.) Where human resources are limited, drugs are imported only through designated ports at which they can be adequately inspected.
- Once the drugs are approved for marketing, samples of drugs in the national drug distribution channels are collected by officials of the national DRA as and when necessary, and are subjected to the necessary quality assessment.
- Noncompliance with drug control laws attracts prosecution and severe penal sanctions and results in the confiscation, forfeiture and destruction of counterfeit drugs when a conviction has been secured.

In countries where, as yet, no official system of product licensing and authorization exists, importation should be controlled by the customs service at the port of entry. Before imported drugs are released for distribution, the importer should present the following documents to the customs authorities:

- a licence/authorization issued to the drug importer
- a licence/authorization for the premises in which the importer operates business related to drugs
- a certificate or licence issued to the qualified person performing the supervisory and/or managerial role on such premises
- the batch certificate for the imported drug
- the bills of lading.

Any imported drugs suspected of being counterfeited should be placed in quarantine pending sampling and analysis in competent laboratories. Drugs confirmed as being counterfeited should be confiscated and destroyed by the national DRA after due process of law.

6.3 Establishing a national drug regulatory authority

Governments should establish a national DRA with the following responsibilities:

- Licensing/authorization of drugs that may legitimately be supplied through the national drug distribution channels. While drug licensing/authorization cannot totally prevent counterfeit drugs in national distribution channels, it can substantially reduce their presence. Imported drugs should be licensed only when there is satisfactory evidence that they are manufactured in establishments with proven records of good manufacturing practice (GMP) and drug manufacturers should be licensed/authorized only if they comply with GMP requirements.
- Establishment of a system of import licensing/authorization for imported drugs. This should ensure that imported drugs are accompanied by certificates complying with the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce.
- Inspection of drug manufacturers, importers, distributors and suppliers as well as producers of packaging materials. There should be sufficient and adequately trained DRA inspectors to control the authorized operations. The inspectors should have authorization: to enter premises and seize any drugs suspected of being counterfeit; and to seal and close premises and establishments suspected of manufacturing, importing, exporting, distributing or selling counterfeit drugs pending prosecution, provided these actions are not contrary to national laws.
- Provision of standard operating procedures (SOPs) and guidelines for the inspection of all licensed/authorized premises and the national drug distribution channels (*21*).
- Development of appropriate procedures for the rapid assessment of suspected counterfeits and the rapid identification and quantification of their active ingredients. Small DRAs should, at least, be able to carry out simple screening methods on drugs and so be able to quantify the active ingredient(s) present.
- Investigation of all reports of drug counterfeiting.
- Dissemination of information on the existence of counterfeit drugs in the national distribution channels, as quickly as possible, to health professionals. The "Drug alert notice" approach could be used when there is a significant hazard to public health.
- Informing the public as necessary, by warnings in the mass media, of the existence of counterfeit drugs in the national drug distribution channels. If possible this should be done without generating panic or causing people unnecessarily to stop taking their medication.
- Prosecution of persons and establishments suspected of manufacturing, importing, exporting, distributing, supplying and selling counterfeit drugs.
- Requiring drug importers to carry out analyses on imported drugs if necessary.
- Provision of adequate training for personnel involved in drug inspection and quality control services and of adequate resources for the optimal performance of their duties.
- Establishment of standard operating procedures for use by licenced/authorized drug distributors/manufacturers should they observe or suspect the presence of counterfeit drugs in the national distribution channels. Procedures for the recall and immediate removal of counterfeit drugs in the national distribution channels should also be established.
- Control of drug movements in free trade zones.

6.4 Developing standard operating procedures and guidelines for drug inspectors

The national DRA should equip drug inspectors with standard operating procedures and guidelines for the inspection of suspected counterfeits (*21*). These should include information on the following:

- examination of documentation
- visual inspection and other nonanalytical checking procedures for the detection of counterfeit drugs
- sampling for analysis, including instructions regarding the size of samples, methods of sampling and procedures for sealing samples and submitting them to the quality control laboratory for full analytical testing
- methods and special precautions for isolating and preventing further distribution of suspect drugs
- the system of recording the actions taken, including basic tests on suspect counterfeit drugs
- methods of seizing and destroying counterfeit drugs, where required.

Random sampling (and testing) is likely to be effective only when the proportion of counterfeits is high; analytical testing is often better used as a confirmatory tool rather than as a primary means of detection. Full analysis of drugs requires suitably-equipped laboratories. Where they do not exist, preliminary data on the quality of drug samples may be obtained using selected basic test methods and thin-layer chromatography techniques. If necessary, suspect drugs can then be sent to subregional or regional quality control laboratories for more detailed quality assessment.

Further guidance on inspection in the drug distribution channels when there is suspicion of counterfeit products is provided in section 8.

6.5 Enforcing drug control laws

Governments should ensure that drug control laws are enforced, clearly specifying the agency or agencies entrusted to enforce those relevant to counterfeiting.

Every effort should be made to identify the sources of counterfeit drugs and to assess their levels in the national drug distribution channels. All reports of counterfeit drugs should be investigated. Workers in the national distribution channels are often favourably placed for early recognition of counterfeit drugs in the marketplace. These workers should be encouraged to be on the alert for counterfeits and to report any suspicion of these to the DRA, which should in turn be able to react rapidly and appropriately to these reports, without detriment to the reporter.

6.6 Empowering the judiciary

Countries should regard the counterfeiting of drugs as a serious offence and their judiciary should be empowered to impose harsh sentences in keeping with the nature of the contravention. Many calls have been made for the imposition of very severe penalties.

Counterfeiting cases should be given priority and handled speedily in the court system, and the courts should be empowered to order the confiscation, forfeiture and destruction of any detected counterfeit drugs.

6.7 Fostering partnerships

The pharmaceutical industry

The pharmaceutical industry has a great part to play in the detection, control and eradication of counterfeiting of drugs. Legitimate drug manufacturers should be encouraged to:

- develop measures, such as the introduction of security systems including the use of security tags, to prevent the counterfeiting of their products
- secure their own stocks of medicines and packaging materials in order to prevent their diversion to illegal manufacturers and packagers
- survey regularly their own and the national drug distribution channels with a view to detecting the presence of any counterfeiting of their products; drug manufacturers whose products have been counterfeited should be encouraged to share this information willingly with the national DRA and law enforcement agents so that it may be used as evidence in court proceedings, in which they could be witnesses
- avoid promoting drugs in a way that results in demands that cannot be met by their own supply system, thereby leaving a gap which could be exploited by counterfeiters.

Importers

The importers of pharmaceuticals should take the necessary steps to:

- ensure that the drugs which they import are being manufactured legitimately in the countries of manufacture
- establish and maintain necessary confidence in the sources of the drugs which they import, and remain satisfied with the integrity and authenticity of the drugs which they import and sell
- be aware of and take into account any security arrangements (such as special printing) used in the country of purchase
- establish and maintain an audit trail of the imported drugs back to the original manufacturer or wholesaler
- obtain certificates for imported drugs that comply with the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce, whenever available
- conduct visual inspection and other analytical checking procedures on the drugs they import to assure themselves of their legitimacy
- maintain records of supplies to wholesale distributors to facilitate recall in the event of counterfeit drugs being detected among their own stocks
- report all relevant details of any detected counterfeit drugs to the national DRA.

Wholesalers and retailers

The wholesalers and retailers of pharmaceuticals should take the necessary steps to:

- purchase drugs from legitimate sources only
- avoid purchasing, selling or supplying any drug suspected of being counterfeit or of which the quality, efficacy or safety are in any way in doubt
- carry out visual inspection and other non-analytical methods of checking the quality of drugs, including checks on the quality of the labelling and packaging materials, and the name and address of the manufacturer
- maintain an audit trail of the drugs they purchase
- in the case of wholesalers, maintain an audit trail of drugs sold to permit the recall of any counterfeit drugs detected, where necessary
- employ suitably qualified persons, preferably pharmacists, to fill supervisory and managerial posts in drug procurement
- report to the national DRA any suspected counterfeit drugs in the national distribution channels; the products concerned should be withheld from supply.

Health professionals

All health care providers should be drawn into the fight against counterfeit drugs. Prescribers should be on the alert for any failure of treatment that might be attributable to a particular drug(s), since this could signal the presence of a counterfeit. The suspected presence of counterfeits should be reported to the national DRA, which should collect and analyse samples.

Associations of health care professionals should encourage their members to use only authorized sources of drug supply. They should establish effective communications with the national DRA for the purposes of exchanging information on suspect counterfeits in the national drug distribution channels. They should also impose severe sanctions on any of their members found guilty of manufacturing, distributing, supplying or selling counterfeit drugs.

Mobilizing the community

Nongovernmental or community-based organizations, such as consumer associations, should be informed about the problem of counterfeiting, and the possible presence of counterfeit drugs in the national drug distribution channels. They should be provided with information on methods of detecting counterfeit drugs and the procedures to follow when making reports to the relevant authorities on any detected counterfeits.

Consumers

The general public should be encouraged to become involved in the fight against drug counterfeiting. Education and information campaigns directed to the public should be established. Consumers should be encouraged to report to the national DRA or the police any suspect products and/or illegal or unauthorized drug manufacturers and distributors they may encounter.

Consumers could also be encouraged to report to their prescribers or physicians: (1) any lack of improvement in their health status in spite of their compliance with prescribed treatment regimens; and (2) all adverse reactions experienced during treatment (unexpected adverse reactions might indicate that the drug used was a counterfeit).

6.8 Sharing responsibilities

Governments, their law enforcement agencies, health professionals, the pharmaceutical industry, importers, distributors and consumer organizations should adopt a shared national responsibility in the fight against counterfeit drugs. Cooperation between all the relevant agencies at the subregional, regional and international levels is also essential for any success in this field.

National level

Cooperation and collaboration between the national DRA and the police and customs services are essential for the purposes of intercepting counterfeit drugs on entry into the country, and the subsequent arrest of offenders. Cooperation between the national DRA, professional health care and consumer associations, the pharmaceutical industry and the general public can make a significant contribution to the identification of counterfeit drugs in national distribution channels. Effective cooperation between law enforcement agencies and the judiciary should also be promoted. The tasks and responsibilities of each agency must be clearly defined and understood by all those concerned.

Governments should ensure that all information on counterfeit drugs in their country is given to those concerned, in particular to the national DRA and police and customs services.

Subregional, regional and international cooperation

Cooperation between countries, especially trading partners, is very useful for combating counterfeiting, in particular to establish and maintain suitable channels of communication among authorities, and to promote training and specialization of personnel. Such cooperation should include the timely and appropriate exchange of information on imported and/or exported drugs, on manufacturers and wholesale distributors, and on the harmonization of measures to prevent the spread of counterfeit drugs. Collaboration would be improved if all countries used the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce for all drug imports and exports. Harmonization of licensing/authorization procedures between countries in the same region should also be encouraged. Countries should explore the possibility of using their diplomatic channels for the exchange of information on counterfeit drugs in international commerce.

Cooperation and collaboration of national DRAs in the same or different regions should be promoted for the purposes of sharing relevant information and for the introduction of harmonized measures to prevent the further spread of counterfeit drugs.

Member States should inform WHO of the existence of any counterfeit drugs in their national drug distribution channels, where necessary requesting that such information be treated as confidential. It is recommended that they should select one person to liaise with counterparts in other countries on the investigation of counterfeit drugs and notify WHO accordingly.

Countries are encouraged to harmonize their drug control legislation with relevant international agreements.

7. Assessment of the Problem at the National Level

As indicated in section 5, it is important to know the magnitude and nature of drug counterfeiting in a country when designing strategies to combat the problem and determining priorities for implementation. The numerous studies conducted in many countries on the quality of available pharmaceutical products were not specifically designed to gather information on counterfeit drugs, and have therefore provided few accurate data in this area. Further information on the risks of exposure to treatments with poor quality drug products and, more specifically, with counterfeit products is also required.

Before embarking on a national study to assess drug counterfeiting, countries should consider appropriate methods and procedures, prepare a practical guide(s) for the collection of samples and decide how the results will be issued. The results of such studies performed in other countries may be useful in designing protocols. If external experts are performing the study, they should discuss all these aspects with the appropriate national authorities prior to implementation.

7.1 Approaches

Methods for obtaining national information on the problem of counterfeit drugs usually include the following steps:

- The collection of background information related to the pharmaceutical sector, in particular, on the drug regulatory system of the country. A questionnaire could be directed to the national DRA (*22*).
- The collection, using random sampling procedures, and analysis of representative samples of selected drugs from the different outlets (see section 7.2).
- The collection of information related to the samples collected, using a questionnaire directed to: the DRA of the country under study, the DRA of the country of origin named on the label, and the manufacturer named on the label (*23*).

7.2 Sampling procedures

In general, the pharmaceutical substances which are to be sampled for testing should be selected according to the following criteria. They should:

- be on the country's list of essential drugs
- be among the most widely used
- be therapeutically important
- be among those most likely to be counterfeited
- include paediatric preparations.

Pharmaceutical outlets and the drugs themselves should be sampled in a random fashion, where possible, and should be representative of the market. Facilities to be monitored should include community and hospital pharmacies, and pharmacies run by missions and other nongovernmental organizations, as well as those in the private sector.

The actual number of tablets or capsules per sample should be decided on the basis of the type of laboratory testing to be performed. In the case of tablets or capsules packaged in strips or blisters, the total number collected should be divided into three equal portions and each sealed. One portion should be sent to the laboratory for testing, one should be sent to the manufacturer for investigation and one should be retained as a control. In the case of tablets or capsules packed in a bottle or similar container, at least two original containers should be sampled. For syrups and injectable powders three portions should be collected. Samples of these products to be sent to the manufacturer through the DRA should be intact and in their original packaging.

The laboratory chosen to perform testing should preferably be a WHO collaborating laboratory.

7.3 Limitations

It is important to be aware of the limitations of country studies. For example, the nature of counterfeiting depends on the specific demand for and availability of certain categories of drugs at any given time in a country. The results of the study may therefore be influenced by the time at which sampling is undertaken.

Random sampling of selected drugs may not necessarily be the best way to find counterfeit drugs, especially if the numbers of counterfeits are few. Moreover, it may be difficult to obtain the required number of samples, or the desired number of sample units from the same batch at one outlet.

The covert purchase of samples from unauthorized outlets may pose serious problems. For example, the vendors may become suspicious of the intent if many samples of one particular batch or batches were sought and purchased. Suspicions might also be aroused if attempts are made to procure samples from more than one outlet in the same area. It is also unlikely that the national DRA could easily obtain the necessary information from the actual manufacturer of the suspected drug.

8. Inspection when Pharmaceutical Products are Suspected to be Counterfeit, Spurious or Substandard

The following guidance was approved by the Thirty-fifth Expert Committee on Specifications for Pharmaceutical Preparations and is reproduced from the Expert Committee's report (*24*). It addresses specifically the situation in which an inspector suspects counterfeit, spurious or substandard pharmaceutical products to be present during an inspection. This may be during either a regular inspection or an investigation aimed at detecting such products.

8.1 Broad objective

The presence of counterfeit, substandard and spurious pharmaceutical products in the drug distribution channels may present a danger to public health. It is imperative that suspect products are effectively and rapidly taken out of the distribution channels and quarantined. In order to facilitate the work of the inspector, the help of capable and experienced persons involved in the distribution of products should be obtained on a proactive basis to help identify such products.

8. 2 Standard operating procedures (SOP)

- A written SOP for inspectors should be drawn up and made available to them. This SOP should include at least the following information:
  - how the suspect product should be isolated to prevent its further distribution
  - the size of the samples required for testing purposes
  - the manner in which the samples should be taken
  - the record-keeping procedure to be followed in recording the details of the action taken
  - the details which should be recorded on the receipt issued for the embargoed product and/or samples taken
  - the type of materials which should be used for sealing samples or for embargoing or confiscating suspect products
  - the names, addresses and telephone numbers of persons who should be contacted to report on the action taken
  - special precautions to be noted by the person initiating the sampling or seizure procedure, with particular reference to correct legal procedures to be followed
  - where appropriate, the manner in which the suspect product should be destroyed.
- Where other persons are involved in the detection of counterfeit pharmaceutical products they shall operate on the basis of a suitable SOP. In any case of suspicion of counterfeit pharmaceutical products an inspector shall be notified immediately.

8.3 Counterfeit products

The following applies specifically to counterfeit products:

- When examining a possible counterfeit pharmaceutical product the inspector shall first screen the product by looking, smelling, touching and listening to the sound of the packing and its contents. The inspector shall look for anything, in particular its labelling and packing, that makes the product look different from an original reference sample. A SOP may assist in examining the product in this way.
- When the organoleptic examination does not give conclusive evidence the inspector shall have a sample tested using appropriate simple screening methods, such as the basic tests recommended by WHO or a suitable thin-layer chromatography method.
- In addition to any full analytical testing, the drug regulatory authority of the country of origin stated on the label of the product may be asked to establish whether the product is counterfeit.
- Proven cases of counterfeit pharmaceutical products shall be fully documented and communicated to all other inspectors, to increase their level of expertise. Information on counterfeit products shall also immediately be made available to drug regulatory authorities of other countries concerned and to WHO.

9. Test methods

In many countries, the quality of industrially manufactured pharmaceutical products is assured primarily through appropriate licensing and inspection systems and by the application of good manufacturing practice (GMP) by manufacturers. Until recently, analytical controls in the drug distribution system were regarded merely as supplemental. Quality surveillance following licensing/authorization was considered as a means of detecting: (1) any unintentional errors in the manufacture of drugs by legitimate producers; and/or (2) any degradation which might occur in the course of normal distribution. Since such events were considered to occur infrequently, heavy sampling was seldom recommended (*25*).

Today, owing to the widespread danger of trade in counterfeit drugs, quality control in the distribution system has acquired new dimensions. When unlicensed/unauthorized products are suspected of being in circulation and adherence to GMP cannot be assumed, a greater number of samples have to be tested in order to maintain an appropriate assurance of drug quality. At the same time, however, pharmacopoeial analyses have become more expensive. The use of simple tests should facilitate a balance between the need to increase the frequency and extent of testing on the one hand, and the need to contain costs on the other. Such first-line simple tests or screening methods would not replace pharmacopoeial, compendial or legally accepted test methods but would identify those products requiring further investigation. No regulatory action could be initiated on the basis of their results, and all samples considered to be potentially counterfeit or substandard would need to be referred for testing according to the pharmacopoeial, compendial or legally accepted reference method(s) to validate the findings of the initial screenings (*7,8*).

The principal requirement for a suitable screening procedure is the identification of the active drug substance. Depending on the capabilities and resources available, this can be achieved through test-tube colour reactions, melting-point determination or thin-layer chromatography (TLC). However, such tests provide only an estimation of the amount of drug substance; any other ingredients, which may be harmful, would not necessarily be detected and quantified. Practical considerations suggest that screening procedures should be performed according to a consistent method, and should have sufficient sensitivity and specificity to permit accurate testing of a large number of products.

Test methods for the detection of counterfeit products will be effective only within the framework of a national DRA with overall responsibility for control of importation and manufacturing procedures for drugs, and the inspection of drug distribution channels.

9.1 Methods based on thin-layer chromatography

TLC screening procedures are recommended for the detection of counterfeit drugs. Numerous studies have demonstrated the multiple uses of these methods. They can be employed for the identification of drug substances, the estimation of drug substance content and the detection of related substances which could be regarded as impurities. TLC procedures are more specific and selective than WHO basic tests for the identification of drug substances (see section 9.2) and are also subject to less interference by excipients.

A counterfeit product may contain the correct active ingredients but in amounts other than those declared. In response to effective anticounterfeit measures, counterfeiters have often introduced small quantities of the genuine pharmaceutically active substances into the dosage forms. This gives positive identification results and in this way counterfeiters attempt to foil or confound the process of detection. In such cases, the basic tests are inadequate; TLC procedures are therefore preferred, as they are capable of giving semi-quantitative information on the active ingredient and also on any related substances in the dosage forms.

9.2 Other simple methods

The WHO basic tests (*26-28*) have provided the basis for the preparation of the testing kits used in the field by various countries.

The basic tests are complementary to TLC methods, and it may be desirable to make use the former in certain cases and the latter in others. The testing laboratory should decide on the method(s) to be used on a case-by-case basis.

9.3 Analytical techniques

Where sophisticated counterfeits are present, testing will require the use of advanced analytical techniques such as mass spectrometry, nuclear magnetic resonance, etc. High-technology techniques, such as those using a near-infrared spectrophotometer, are also useful. The apparatus is simple to operate and can be used for the identification and semi-quantification of active ingredients in dosage forms. It is available as a portable unit requiring a very small amount of sample and little sample preparation, and gives results in a matter of minutes with the help of computerized controls. While the initial cost of such technologies may be an inhibiting factor, this should be weighed against the advantages they provide in terms of quick and accurate detection of counterfeit drugs. It should also be considered against the costs of training personnel in other methods and of acquiring and maintaining the supplies of reagents and other special materials required for those methods (29).

9.4 Visual inspection

Irrespective of the analytical method used, the first step in identifying potential counterfeit drugs is the careful visual inspection of the product, and its packaging and labelling. A comparison with the authentic drug product is always preferred. Differences in labelling, packaging and the physical appearance of dosage form, e.g. shape, colour, etc., indicate a potential counterfeit (*8,9,24*).

Even in the absence of knowledge of the physical characteristics of the authentic drug, a visual inspection may indicate that there has been tampering, that there is non-uniform colouration of the drug product under investigation, etc. Again such observations signal the possibility of a counterfeit.

Legitimate drug manufacturers should be encouraged to collaborate with national DRAs and with WHO by providing information and materials on the physical attributes of their products; this would be also be to their own benefit.

9.5 Successful implementation of simple tests

The following points should be taken into consideration:

- The costs of performing simple and other tests for the detection of counterfeits should be weighed against the larger costs of drug injury, ineffective therapy and possible patient deaths.
- Guidelines for official organoleptic detection procedures should be widely available to all relevant persons. Pharmaceutical manufacturers should be encouraged to collaborate with national DRAs in the provision of information and appropriate materials dealing with the physical attributes of their products.
- All available technical documents should be translated into the official/national language(s).
- Consideration should be given to the application of rapid quantification procedures when counterfeit products have been positively identified.
- The type of systems to be used should be carefully considered before anyone is selected for training in counterfeit testing. Some methods, e.g. high-performance TLC, are sophisticated and have proved too difficult for less qualified personnel in previous training programmes.

10. Developing Training Programmes: Inspection and Examination of Counterfeit Pharmaceuticals

The following guidelines are a modified version of the provisional guidelines for developing training programmes approved by the Thirty-fifth Expert Committee on Specifications for Pharmaceutical Products (*30*), and subsequently considered by the International Workshop on Counterfeit Drugs (*12*).

10.1 General remarks

Introduction

The detection and prosecution of criminals who market counterfeit pharmaceuticals have several stages. First of all, suspect products have to be traced. The drug, sampled according to an established procedure, should undergo defined physical or organoleptic examination by the drug inspector. If the results indicate that the drug formulation may be a counterfeit product, then at least some chemical tests must be repeated to confirm the necessity for further analysis. Drugs are then analysed by simple tests, including TLC. If these tests do not provide conclusive evidence and the drug is still considered to be a possible counterfeit, then a compendial procedure is required.

Throughout the investigation, it is assumed that a chain of custody has been established, i.e. the correct procedures were followed before the drug was received for analysis by the laboratory. This ensures that the results of these examinations are reliable and will be accepted as valid in future steps, e.g. prosecution of the supplier of the counterfeit pharmaceuticals. The final results shall be submitted to the appropriate official in the drug regulatory authority.

Section 10.2 describes the training necessary for inspectors. Section 10.3 describes training in the design and implementation of a specific programme for the screening of counterfeit pharmaceuticals. There are several common requirements for both inspection and chemical testing, and these are included as items in the training programmes for inspection and examination of counterfeit pharmaceuticals. It is assumed that the trainers are already suitably experienced to perform the required inspection, examination and training. The two-tiered approach of the training programme should include training of trainers, who in turn educate those who need to be trained in drug inspection and examination. The main focus of these guidelines, however, is the training of the trainees.

The practical issues to be considered in the organization and implementation of the programme are described in section 10.4.

Each country must develop its own strategy, appropriate for its situation, the availability of an institutional framework, and its professional and economic resources. Ideally it should be prepared by the country's drug regulatory authority, in consultation with all major parties involved in the manufacturing, importation, distribution, sale, prescribing and use of legitimate drugs.

Requirements and goals of the training programmes for inspection and examination

An effective approach to the detection and prevention of counterfeit pharmaceuticals requires professional competence of the personnel, motivation, and awareness of the problems.

The ultimate goals of the programme should be:

- to raise the morale of professionals involved in drug inspection and examination
- to establish a control system to prevent the flow of counterfeit pharmaceuticals into the legitimate distribution channel.

These goals cannot be achieved without the concerted effort of other programmes concerned with improvement of the pharmaceutical infrastructure. In order to ensure the quality, safety and efficacy of drug products accessible to the target population, a secured and satisfactory drug distribution system is required.

Prerequisites

The primary prerequisite for any programme combating pharmaceutical counterfeiting is the existence of an established drug regulatory authority in the country (*31*). That implies the existence of at least the following:

- A legal framework. The legislation is expected to cover criminal activity in relation to the manufacture, import, distribution, sale and dispensing of counterfeit pharmaceuticals. The act of counterfeiting should be an offence such that the inspector of drugs, the police and other investigating agencies are all able to take action. The law should also provide for deterrent punishments.
- A system requiring:
  - licensing/authorization of manufacturers, importers, distributors, retailers and pharmacies
  - licensing/authorization for marketing of drugs
  - proper labelling.
- Adequate professional staff and resources within the DRA.

10.2 Training programme on inspection

Course objectives

The aim of this course is to provide trainees with:

- an awareness of methods for the detection of counterfeit pharmaceuticals
- an understanding of the difference between counterfeit and substandard pharmaceuticals
- the ability to evaluate the test data
- the ability to distinguish between normal and suspect pharmaceuticals on the basis of physical aspects

- the ability to identify reports of adverse effects or lack of efficacy that might result from the use of counterfeit pharmaceuticals
- the ability to justify their actions in the legal context of detection and prosecution including the prosecution of offenders, independently, if so authorized, or by the appropriate authority
- an awareness of methods of making the legitimate distribution system secure, e.g. by a system of warranty or, for international trade, by compliance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*16*)
- a knowledge of how to share information, coordinate and collaborate with all concerned in combating counterfeit pharmaceuticals.

Types of training

The training of inspectors consists of conveying theoretical and background information by lectures and discussion of case studies. Furthermore, the training course should contain practical examples and field work. Training will also cover the organoleptic inspection of products, including examinations of products when available.

Educational background of trainees and trainers

This training is aimed at inspectors, preferably with some experience in the inspection of drugs. Guidance as to what level of experience is expected can be found in the "Guidelines for inspection of drug distribution channels" (*21*). Training covering counterfeit pharmaceuticals should be included in all basic training courses for inspection.

The trainer should be experienced, have full knowledge of general and official inspection methods, and should be able to conduct and design, when necessary, the training programme for the trainee. Other characteristics include:

- previous experience with detection and prosecution procedures
- an appreciation of the inspector's role in the legal system for combating counterfeit products
- an understanding of the difference between counterfeit and substandard pharmaceuticals
- knowledge of the latest statistics on the prevalence of counterfeit pharmaceuticals in the country, if possible
- knowledge of relevant quality standards
- thorough overall knowledge of the subjects to be taught.

Course programme items

The following items should be included in the course; the actual content of each item will depend on the trainees' prior experience (see Box 3).

Box 3

Course programme items for inspectors

- overview of relevant legislation
- national drug regulatory systems, inspection and quality control
- drug distribution systems
- illegal distribution channels
- types of counterfeit pharmaceuticals encountered
- general characteristics of various dosage forms, such as active ingredient to excipient ratio in tablets, capsules, ampoules, powder for injection, ointments, creams, etc.
- factors leading to the manufacture and sale of counterfeit pharmaceuticals (e.g. profit)
- measures to detect counterfeiting (e.g. checking records of distributors and measurement of various physical properties of the product, labelling features, packaging materials and packaging of various drug forms)
- methods of market surveillance for detection of counterfeit pharmaceuticals at the import, manufacture, distribution and sales levels, based on intelligence services and visual examination of samples
- organizing sample collection
- sample and test report handling
- preparation for prosecution by:
  (*a*) investigation of cases to identify the suspect persons responsible for the offence
  (*b*) collection of legal evidence for proceedings in the courts
  (*c*) maintaining a system of security of evidence including persons and case property
- prosecution of offenders
- proper follow-up of the cases
- development of a network of informants
- education about the system to ensure distribution and sale only of legitimate products in the market, e.g. system of warranty
- familiarization with the methods of information sharing, coordination and collaboration with all concerned in combating counterfeiting. These include other inspectors, health professionals, and representatives of the pharmaceutical industry, police and other investigating agencies at the national, and where necessary, at the international level
- relations between the pharmaceutical inspectorate and other law enforcement agencies, such as customs, police, health inspectorate, veterinary inspectorate, legal departments
- relations with drug manufacturers at home and abroad
- relations with WHO, including reporting to and being informed by WHO, through the national drug regulatory authorities

Box 3
Course programme items for inspectors
(continued)

- reference data in books or electronic form (e.g. Internet)
- security aspects
- record-keeping, the importance of properly documented standard operating procedures, including description of samples according to a defined model
- preparation of official reports.

Course programme items may vary according to the specific requirements of each country. Further guidance may be found in the "Guidelines for inspection of drug distribution channels" (*21*).

Duration of training course

The duration of the course depends on the local situation. A typical course may last one week.

Reiterative training

Refresher courses should be regularly organized and attended. Country demand would determine the frequency of these courses.

Assessment

Continuous assessment will be conducted during the programme.

Certificate

An appropriate certificate should be issued on satisfactory completion of all parts of the programme.

Evaluation of the programme

Evaluation is an important component of any such activity, particularly since the occurrence and nature of counterfeiting differ from country to country. This may result in changes in the activities of inspectors. Therefore, a refresher course could be of a different nature, if so indicated by evaluation.

Document kit

Trainees should be provided with a document kit which should include references (*2-5*),(*12*),(*16*),(*20*), (*21*) and (*31-34*).

10.3 Training programme on examination

Course objectives

The aim of this course is to provide trainees with:

- an awareness of the importance of examining suspect pharmaceuticals in order to facilitate the inspector's decision whether or not to act
- sufficient knowledge and skills to examine counterfeit pharmaceuticals
- an understanding of the difference between counterfeit and substandard drugs
- knowledge of the value and limitations of techniques for rapid examination, and the ability to make rational decisions about their use
- the ability to justify legal action in the context of detection and prosecution.

Types of training

Theory and practice involving examination of drugs.

Educational background of trainees and trainers

Previous or formal training of trainees is not absolutely required for the examination of drugs, but former training would be advantageous. Preferably, trainees should meet the following criteria, according to country requirements:

- knowledge of and competence in selected laboratory techniques, such as using a weighing balance and volumetric measurements, and the ability to perceive differences in colours
- reading and writing skills to facilitate adequate record-keeping
- an understanding of the need and the willingness to work as a team and to share information.

The trainer should be experienced and have full knowledge of general and official analytical methods. Furthermore, he or she should be able to conduct and design, when necessary, the training programme. Other characteristics include:

- an appreciation of the role of chemical testing in the legal system for combating counterfeit products
- an understanding of the difference between counterfeit and substandard drugs
- knowledge of the latest statistics on the prevalence of counterfeit pharmaceuticals in the country, if possible
- knowledge of relevant quality standards
- knowledge of characteristics of various dosage forms
- thorough overall knowledge of the subjects to be taught.

Course programme items

The following items should be included in the course; the actual content of each item will depend on the prior experience of the trainees (see Box 4).

Box 4
Course programme items for examiners

- overview of relevant legislation
- national drug regulatory systems, inspection and quality control
- drug distribution systems
- illegal distribution channels
- types of counterfeit pharmaceuticals encountered
- general characteristics of various dosage forms, such as active ingredient to excipient ratio in tablets, capsules, ampoules, powder for injection, ointments, creams, etc.
- sampling methods
- reference substances and working standards: importance and maintenance
- reference data in books or electronic form (e.g. Internet)
- security aspects
- record-keeping, the importance of properly documented laboratory work including description of samples
- preparation of official reports
- relations with WHO
- examination techniques (see below)

After demonstration of the techniques to be used, trainees should practice with an adequate number of known dosage forms, preferably including capsules, tablets, injectable preparations and ointments. Trainees will then test unknown samples, report on their work and draw conclusions as to whether the samples are counterfeit or require additional analysis. The results will be compared with previously determined data and will be discussed in the group.

In the course, the trainee will be taught to perform various examinations including:

- examination of labelling features, packaging materials and packaging of various drug forms
- measurement of various physical properties of the product
- thin-layer chromatography
- other specifically selected examination procedures.

Duration of course

Duration of the course depends on the local situation. A typical course would take about 10 days, consisting of:

- introduction (1–2 days)
- theory (1–2 days)
- practical work in the laboratory and field, if necessary on various dosage forms (4 days)
- preparation of a summary and reporting (2 days).

Reiterative training

Refresher courses should be regularly organized and attended. Country demand would determine the frequency of these courses.

Assessment

Continuous assessment will be conducted during the programme.

Certificate

An appropriate certificate should be issued on satisfactory completion of all parts of the programme.

Evaluation of the programme

Evaluation is an important component of any such activity, particularly since the occurrence and nature of counterfeiting differ from country to country. This may result in changes in the activities of inspectors. Therefore, a refresher course could be of a different nature if so indicated by evaluation.

Document kit

Trainees should be supplied with a document kit which should include references (*26*)-(28) and (*32*).

10.4 The practical issues of organizing and implementing the programme (*35*)

Getting started

Establish a core group for organizing the training programmes

- Organize the core group for planning and implementing the education programme. The group may be organized by health authorities, or by nongovernmental organizations or joint enterprises.
- Establish roles and responsibilities for all participants in planning and implementation.

Develop the profile of what is required and estimate the output of the programme

- Construct the profile of the required system of national or local drug distribution in terms of the characteristics of both professionals and the general public.
- Collect data regarding the target professionals.
- Assess the overall performance of the target professionals.
- Identify the extent of the combating responsibility of the target professionals in counterfeit pharmaceuticals.
- Identify what the professionals need to improve their performance in combating counterfeit pharmaceuticals, and prioritize according to the available resources.
- Identify the "end products" to be achieved by the training programme.

Plan the curriculum according to the need

- Develop a survey of the needs.
- Identify sources of data and other resources.
- Prepare a plan (who, where, when) for collecting data.
- Collate information.

Assess the facilities and staff available

- Assess the available teaching staff, equipment and facilities in institutions for training.
- Determine whether additional staff and equipment will be needed to meet the objectives and provide the curriculum as planned.

Work with other concerned parties

- Identify institutions, groups and persons in the community with whom to collaborate.
- Share information with these institutions, groups and persons in order to encourage collaboration in the programme.
- If there are not enough resources available in the target area, find resources outside the area.

Select the target groups

- Identify the target professionals and select the core groups for whom the programmes will be most effective.
- Ensure that the distribution of participants in the training programme is balanced in terms of disciplines and regions.

Initiating implementation

Secure financial support

- Investigate potential and existing internal and external sources of financial support for the programme.

Gather materials for a curriculum

- Contact institutions, agencies and other organizations with experience and expertise in the pharmaceutical training fields, including WHO and its collaborating centres.

Make arrangements for the trainees

- Arrange accommodation and travel for the trainees, if necessary.

Recruit teaching staff

- Contact and recruit suitable teaching staff.
- Arrange their accommodation and travel, if necessary.

Establish a positive image for the goal of the programme

- Identify core trainees who understand the meaning of the programme and support it.
- Obtain early support by key persons.

Deal with barriers

- Attempt to overcome resistance to the programme (e.g. reluctance to take up the issue of counterfeit pharmaceuticals).

11. Conclusion

In considering measures against counterfeit drugs, emphasis should be given to the following:

The establishment of an adequate national drug regulatory system – an essential starting point. The system should include licensing/authorization of pharmaceutical products. It should also cover licensing/authorization of manufacturing, importation and distribution practices and premises and adequate inspection arrangements. It is the responsibility of governments to ensure that counterfeit drugs are taken off the market, and their sources found and eradicated. This should be a part of their overall quality control system.

Shared responsibility among the relevant parties. At the national level any difficulties and inefficiencies should be overcome by cooperation between the government agencies concerned and also with other involved groups. At the international level Member States, WHO, other United Nations organizations, nongovernmental organizations and other interested bodies should collaborate in the detection and prevention of counterfeit drugs. In this context, the liaison officers for the anticounterfeit pharmaceuticals network should be utilized to ensure timely exchange of information.

Sharing of information on counterfeit drugs with other countries and WHO. Where counterfeit drugs present the risk of serious health consequences, such information should be urgently and widely disseminated, in particular to the DRAs concerned.

Adequate training by government of the personnel of the national DRA and other relevant agencies involved in detection of counterfeit drugs.

Use of the measures and tools presented in these guidelines – by government and related parties to further combat counterfeit drugs.

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Glossary

The definitions given below apply specifically to the terms as used in these guidelines; they may have different meanings in other contexts.

Batch
A defined quantity of any drug processed in a single process or series of processes such that it is reasonably expected to be uniform in character and quality.

Batch certificate
A document containing information, as set out in Appendix 3 of the Guidelines for Use of the WHO Certification Scheme (*16*) , will normally be issued for each batch by the manufacturer. Furthermore, a batch certificate may be exceptionally validated or issued by the competent authority of the exporting country, particularly for vaccines, sera and other biological products. The batch certificate accompanies every major consignment.

Drug (medicine, pharmaceutical product, pharmaceutical)
Any substance or mixture of substances that is manufactured for sale or distribution, offered for sale, sold, supplied or presented for use in:

(i) the treatment, mitigation, cure, prevention or diagnosis of disease, an abnormal physical state or the symptoms thereof in humans or animals
(*ii*) normal physiological conditions in humans or animals; or
(*iii*) the restoration, correction or modification of organic functions in humans or animals, or any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient.

Drug regulatory authority
The national agency responsible for the registration of and other regulatory activities concerning pharmaceutical products.

Good manufacturing practices
That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization/product licence.

Manufacture
All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products and the related controls.

Manufacturer
A company that carries out at least one step of manufacture.

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[1]The terms "drug", "medicine", "pharmaceutical product" and "pharmaceutical" are used interchangeably in these guidelines.

Marketing authorization
An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, *inter alia*, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using international nonproprietary names or national generic names where they exist), the shelf-life and storage conditions and packaging characteristics. It also contains information approved for health professionals and the public, the sales category, the name and address of the licence holder, and the period of validity of the licence.

National drug distribution channels
Facilities through which drug products are distributed within a country.

Packaging
All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Pharmacist
The holder of a degree or diploma in pharmacy from a recognized higher institution of learning who is registered or licensed to practise pharmacy.

Quality control
That part of good manufacturing practice concerned with sampling, specifications and testing and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.