WHO Global Surveillance and Monitoring System

for Substandard and Falsified Medical Products

World Health Organization

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ISBN 978-92-4-151342-5

Suggested citation. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Printed in Switzerland

Design and layout by Jean-Claude Fattier

ABBREVIATIONS

Gavi	The Vaccine Alliance
GMP	Good manufacturing practices
GSMS	Global Surveillance and Monitoring System for substandard and falsified medical products
ICG	International Coordinating Group
NGO	Nongovernmental organization
NMRA	National or regional medicines regulatory authority
UNICEF	United Nations Children's Fund
US FDA	United States Food and Drug Administration
WHO	World Health Organization

ACKNOWLEDGEMENTS

We are grateful to the United States Food and Drug Administration, the European Commission (ACP-EU Partnership), Asian Development Bank, United States Pharmacopeia and the Bill and Melinda Gates Foundation for their contributions.

We are also grateful to the Member States, as well as the many delegates and trainers, among others, who have participated and assisted in various workshops and meetings.

Special thanks are due to the following organizations and their staff who contributed time and expertise, and also for their assistance in managing and reporting incidents.

Agence nationale de sécurité du médicament et des produits de santé, France; Agência Nacional de Vigilância Sanitária, Brazil; Asia-Pacific Economic Cooperation; Badan Pengawas Obat dan Makanan, Indonesia; Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices), Germany; Bundeskriminalamt Wiesbaden, Federal Crime Police Office, Pharmaceutical Crime, Germany; Dirección Nacional de Vigilancia Sanitaria, Paraguay; Ecumenical Pharmaceutical Network; Food and Drugs Authority, Ghana; Food and Drugs Authority, United Republic of Tanzania; Fundação Oswaldo Cruz; German Institute for Medical Mission, Difäm; Georgia Institute of Technology; Institut Pasteur de Dakar; Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit; London School of Hygiene & Tropical Medicine; Médecins Sans Frontières; Medicines and Health Products Regulatory Authority, Liberia; Medicines and Healthcare products Regulatory Agency, United Kingdom of Great Britain and Northern Ireland; Ministry of Health, Israel; Mission for Essential Drugs and Supplies, Kenya; Ministry of Health, Labour and Welfare, Japan; National Agency for Food and Drug Administration and Control, Nigeria; National Institute for Public Health and the Environment, Netherlands; Paul Ehrlich Institute, Germany; Punjab Forensic Science Agency, Pakistan; Punjab Institute of Cardiology, Pakistan; The Global Fund to Fight AIDS, Tuberculosis and Malaria; TouchstoneCRM; United Nations Children's Fund; United Nations Development Programme; United States Food and Drug Administration, United States of America; United States Pharmacopeia, Promoting the Quality of Medicines Program; University Medical Center Utrecht; University of Notre Dame; Uppsala Monitoring Centre.

We are thankful to all of the Member States and their national medicines regulatory authorities who hosted regional and national training events in the following countries: Argentina; Ethiopia; India; Myanmar; Nigeria; China (People's Republic of); Indonesia; Senegal; Singapore; Switzerland; Thailand; Philippines; Tunisia; Turkey; United Republic of Tanzania; Zimbabwe.

Finally, we are indebted to all national regulatory focal points. Without their notifications, this report would not have been possible.

Author

Dr Elizabeth Pisani, Associate Professor, London School of Hygiene and Tropical Medicine.

WHO Secretariat

Dr Suzanne Hill, Ms Emer Cooke, Dr Clive Ondari, Mr Michael Deats, Ms Pernette Bourdillon Esteve, Ms Diana Lee, Ms Lisa Greenough.

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A CASE IN POINT

In September 2013, a hospital in Paraguay admitted 44 children in quick succession. All of them had difficulty breathing – six were so badly affected that they were taken to intensive care. Hospital staff could not immediately identify the cause of the outbreak; they feared some unrecognized disease. National authorities began to investigate straight away. They found that the condition always started with symptoms of the common cold, which parents had treated with locally-made cough medicines.

The national medicine regulator alerted the World Health Organization (WHO), and the information was passed on to the WHO Substandard and Falsified Medical Products Group in Geneva. The story was worryingly familiar to that team who had seen a similar case in a completely different part of the world: Pakistan.

In that earlier case, 60 adults in two cities in Pakistan had died after consuming large quantities of cough syrup as part of their drug addiction. The Government of Pakistan had acted quickly to suspend production of the medicine by two local manufacturers (Fig. 1). Both manufacturers had recently changed their source of active pharmaceutical ingredient to a cheaper one. The authorities in Pakistan recalled the remaining stock and the active ingredient, dextromethorphan, which had been imported from India. Indian authorities were notified and they suspended production until the cause of the problem was established. But initial laboratory test results were confusing. The medicines appeared to contain the correct amount of dextromethorphan; there was no clear indication of why patients taking it had died.

Authorities in Pakistan requested WHO to help to investigate further. Tests in laboratories overseas revealed that, together with the advertised ingredients, the cough syrup contained levomethorphan, a more powerful drug with the same molecular formula as dextromethorphan, but a different chemical structure. Ironically, the investigation was slowed down by laws designed to keep us safe: levomethorphan is about five times stronger than morphine and its sale is tightly regulated, so very few laboratories have reference samples that can be used for comparison to suspect products and movement of those samples is strictly controlled.

Ten months later, Paraguay seemed to be facing a similar crisis. Although the cough medicines were made by different companies some 15 300 kilometres and two continents apart, WHO immediately knew where to start looking. They also knew that unless they acted quickly, patients could die.

FIG. 1: BOTTLES OF COUGH SYRUP CONTAINING LEVOMETHORPHAN THAT CAUSED DEATHS IN PAKISTAN 2012-13

Paraguayan investigators went to the factory where they found import records for the dextromethorphan in the cough medicines the sick children had taken. A quick check against the WHO substandard and falsified medical products database showed that it came from the same Indian manufacturer that had supplied the factory in Pakistan; indeed, it had the same batch number. Within days of reporting their concerns, doctors in Paraguay were able to treat their patients with an antidote to levomethorphan and, because of this quick action, the patients survived.

WHO provided support to investigate the incident more thoroughly, and issued a second alert listing the batch numbers of all the dextromethorphan that might have been contaminated. It had been exported to several countries in Europe, north Africa, the Middle East and Latin America. Companies in both Colombia and Peru had already used the contaminated chemical to make cough medicines. However, they were alerted to the danger before any of their products reached patients, and were able to recall them, averting potential hospitalizations and deaths. However, the batches that reached the Middle East were never traced.

This case highlights a stark reality: global supply chains require a global system that can quickly alert people worldwide to the danger posed by substandard and falsified medical products. More than that, it highlights the urgency of the task: the consequences of failure can be fatal.

1. INTRODUCTION

The contaminated cough medicine provides a clear illustration of the worrying problem of substandard and falsified medical products, a problem that appears to be growing as global supply chains become more complex and e-commerce spreads. This report, based on data gathered by the World Health Organization (WHO) Global Surveillance and Monitoring System for substandard and falsified medicines, vaccines and in vitro diagnostic tests (GSMS) during its first four years of operation, up to 30 June 2017, examines the issue in greater detail.[1]

Chapter 2, "Substandard and falsified medical products: the consequences" outlines the impact that substandard and falsified medical products can have on individuals, families, national health systems and the economy. Although it is not yet possible to quantify these impacts accurately, Chapter 3 presents data from the surveillance system and other sources that give a clearer indication of the distribution of the problem, and its reach into health systems. It shows that some of the medical products that are most important for maintaining the health of people at all income levels and facing many different health threats, are currently being poorly produced, stored or transported, or falsified.

The core of the report, Chapter 4, describes the forces that drive the trade in these dangerous products, showing how they reach patients and consumers. The cases presented in this report to illustrate these factors are drawn from the 1500 so far reported to the WHO substandard and falsified medical products surveillance database.[2]

Chapter 5 discusses the systems and actions needed to prevent, detect and respond to the threat posed by substandard and falsified medical products. It describes action being taken across WHO and by countries in conjunction with other key partners to minimize the trade and the risks it poses. This chapter also explains how the WHO GSMS for substandard and falsified medical products is building a global evidence base that underpins effective action. Conclusions are drawn in Chapter 6.

WHO's new surveillance system was developed after it became clear that globalized production chains and the increasing interconnectedness of the medical products market would be a game changer in oversight of the medicines supply chain. No country or region working alone could easily collect all the information it needed to respond rapidly to threats from substandard and falsified medicines. Building on an initiative developed in the WHO Western Pacific Region, the GSMS was born. Principally funded by the United States Food and Drug Administration (US FDA), with support from the Bill and Melinda Gates Foundation and with training events supported by the European Commission, Asian Development Bank and United States Pharmacopeial Convention, it was piloted in 10 countries in 2012 and 2013, and launched in Africa in July 2013. The system aims to work with WHO Member States to improve the quality of reporting of substandard and falsified medical products, and, importantly, to ensure the data collected are analysed and used to influence policy, procedure and processes to protect public health, at the national, regional and the global level (Box 1).

[1] For the sake of concision, we refer to medicines, vaccines and diagnostic kits collectively as "medical products".

[2] The selection of cases does not reflect the prevalence of substandard and falsified medical products in different markets. Rather, they were chosen because each provides a good illustration of a particular factor driving the trade in these products.

BOX 1: WHO Global Surveillance and Monitoring System for substandard and falsified medical products (GSMS)

PROCESS:

Step 1. Reports of suspected substandard or falsified medical products "submitted by public, health care professionals, industry, supply chain, customs, police, procurers and nongovernmental organizations to the national or regional medicines regulatory authority (NMRA)

Step 2. Assessment and response by NMRA

Step 3. NMRA Focal Point searches and reports to WHO's surveillance and monitoring system database

Step 4. Immediate technical assistance and alerts are issued by WHO when requested and appropriate. Validated reports and data inform policy, procedure, processes, investment and the work of the Member State mechanism

Key achievements as of July 2017:

- 17 WHO training workshops conducted
- 126 Member States and more than 400 regulatory personnel trained
- 18 of the largest international procurement agencies sensitized to the issue
- more than 1500 product reports
- 20 medical product alerts and numerous warnings
- WHO portal accessible in multiple languages to nominated focal points from regulatory agencies, who provide reporting and database search tools
- mobile phone application designed to improve information flows for NMRAs when detecting and reporting substandard and falsified medical products.

This report has grown out of the work of the GSMS, which provides national regulatory authorities with an interconnected network. This allows them, for the first time, to cross-reference reports of suspect products with those reported from other regions by searching the WHO database and accessing photograph libraries of confirmed substandard and falsified products. It links incidents and countries, which not only assists regulatory authorities but ultimately can have beneficial outcomes for patients, as seen in the case in Pakistan and Paraguay.

As the system grows it will provide an ever richer evidence base, allowing countries to pinpoint risk situations more efficiently, and to respond more rapidly to protect their citizens from substandard and falsified medical products. As a case reporting system, the data from the GSMS is representative only of those products detected and reported by the focal points, and cannot be extrapolated to determine the overall magnitude of the problem. Data on prevalence and cost is vital to not only strengthen the public health case to focus interventions and investments, but to meaningfully engage with other multisectoral stakeholders including policymakers.

Therefore, this report is published together with a WHO Study on the public health and socioeconomic impact of substandard and falsified medical products which examines published surveys of the quality of medicines from the past decade to provide overall estimates on the scope, scale and harm. It commissions two additional studies to inform models of the impact of substandard and falsified medical products in two specific areas: childhood pneumonia and malaria. The study estimates the observed failure rates of substandard and falsified medical products in low- and middle-income countries at approximately

10.5%. If this is applied to unweighted estimates of market size in low- and middle- income countries, the estimated spend is in the order of US$ 30.5 billion. If this is even approximately correct, it highlights the urgent need to address this problem.

The challenges posed by the manufacture and trade in substandard and falsified medical products are very great and likely to grow. However, international coordination mechanisms and political leadership on this issue are also growing dramatically, supported by an expanding global evidence base. As can be concluded in Chapter 6, the opportunities for preventing, detecting and responding to the challenge effectively have never been better.

BOX 2: What are substandard and falsified medical products?

For many years, the response to this important threat to public health was embroiled in the discussion of complex definitions that meant different things to different people. Reflecting this complexity, until May 2017, WHO used the term "substandard/spurious/falsely-labelled/falsified/counterfeit medical products" (SSFFC). The WHO Member State mechanism on SSFFC medical products was tasked with revising these definitions to ensure that they were based on a public-health perspective, with no account taken of intellectual property concerns. Based on their deliberations, the World Health Assembly, which governs WHO, adopted the following definitions:

Substandard medical products

Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or their specifications, or both.

Unregistered/unlicensed medical products

Medical products that have not undergone evaluation and/or approval by the NMRA for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

Falsified medical products

Medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Source: Appendix 3 to Annex, World Health Assembly document A70/23, 2017.


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2. SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS: THE CONSEQUENCES

In some senses, growing concern about the quality of medicines and other medical products (such as vaccines and diagnostic kits) is the result of the world's partial, and still inequitable, success in increasing access to medical care. Far too many people in the world still have no access at all to basic health care. Up to two billion people cannot get medicines that are crucial for their health (*1*), and many millions more risk being tipped into abject poverty by health care costs that they simply cannot afford. As this report shows, constrained access to quality, safe and effective medical products creates a vacuum that is too often filled by substandard and falsified products.

Despite this huge and continuing challenge, efforts to reduce global inequities in access to health care have succeeded at least partially. Per capita spending on health more than doubled worldwide in the 20 years to 2014, the last year for which comprehensive data are available (*2*).[3] In low-income countries, spending on health came close to tripling over those two decades. Although much of that still comes out of the pockets of families who can ill-afford it, the percentage of the health care bill paid by governments rather than families is rising fastest in the poorest countries.

One effect of these collective successes is that the market for medicines and other medical products has shown unprecedented growth. Some 15 years ago, global sales of medicines rose above US$ 500 billion for the first time. Since then, sales have doubled again, to approximately US$ 1.1 trillion, with by far the largest growth occurring in middle-income markets (*3,4*). Unfortunately, this growth has opened the door not just to quality, safe and effective medicines, but also to medicines, vaccines and other products that do not meet quality standards and that are sometimes positively dangerous.

As detailed in Box 2, substandard medical products are made by registered manufacturers. However they do not meet approved quality standards, sometimes because they were poorly manufactured, or badly packaged or transported. In the case of falsified medicines, the manufacturing and packaging are deliberately designed to deceive consumers. These items, masquerading as medical products, may contain amounts of active ingredient that are either dangerously high or ineffectively low. They may contain contaminants (as was the case with the cough medicines in Pakistan and Paraguay), or no active ingredient at all. Sometimes, medicines that have passed the expiry date determined by manufacturers and regulators are repackaged and put back on the market, sometimes pretending to be a completely different medicine. These irregularities can undermine people's confidence in medical systems and endanger health, while eating into family and government budgets.

2.1 A significant threat to health

When medicines do not work the way they should (as is the case with most substandard and falsified medical products), they can prolong illness and the inconvenience, time off work and often the misery that go with it. Doctors and other health workers waste precious time trying out alternative treatments, when all that is really needed is a quality version of the same treatment. In the worst cases, several of which are described in this report, people die, either from untreated disease or because the product itself kills them.

[3] Per capita expenditure on health, calculated at purchasing power parity (https://data.worldbank.org/data-catalog/health-nutrition-and-population-statistics, accessed July 2017).

2.2 Promoting drug-resistant infections

Substandard and falsified medical products in one country can make diseases impossible to treat even in another country that has a very well-regulated medicine market. This is because substandard medicines promote antimicrobial resistance. Antibiotics and other antimicrobial medicines are manufactured and prescribed at doses designed to destroy the pathogens that are causing illness. If a treatment course contains only a fraction of the correct dose, or if it is so badly made that the active ingredients are not released properly, then it is only likely to destroy some of the pathogens, but not all of them. The ones that survive will be the ones that have mutated enough to survive low doses of the medicine. Usually, they do not reproduce very quickly. But with all the more susceptible strains killed by the weak medicines, they have room to multiply and spread to more people. There is clear evidence that resistance to the most important antimalarial medicine, artemisinin, first appeared in a part of the world where at one point between 38 and 90% of the artemisinin medicines on the market were substandard or falsified (*5*–*7*).

This really is a global problem. In the age of cheap air travel and mass population movements, people who develop resistant infections because of substandard or falsified medicines in one country can easily travel to another country and pass on the mutant infection. Once a bacteria or virus is resistant to a medicine, even a full treatment course will not kill it. So even if the medicines in the new host country are all perfect quality, they will not cure the disease. This not only affects treatments for tropical diseases like malaria. Essential antibiotics are used for routine purposes on every continent, for example to prevent infection in cancer patients whose immune responses are temporarily reduced because of chemotherapy, or to protect against infection during planned surgery. Substandard and/or falsified versions of these antibiotics have also been reported in every region of the world.

2.3 Complex supply chains: a gateway for falsified products

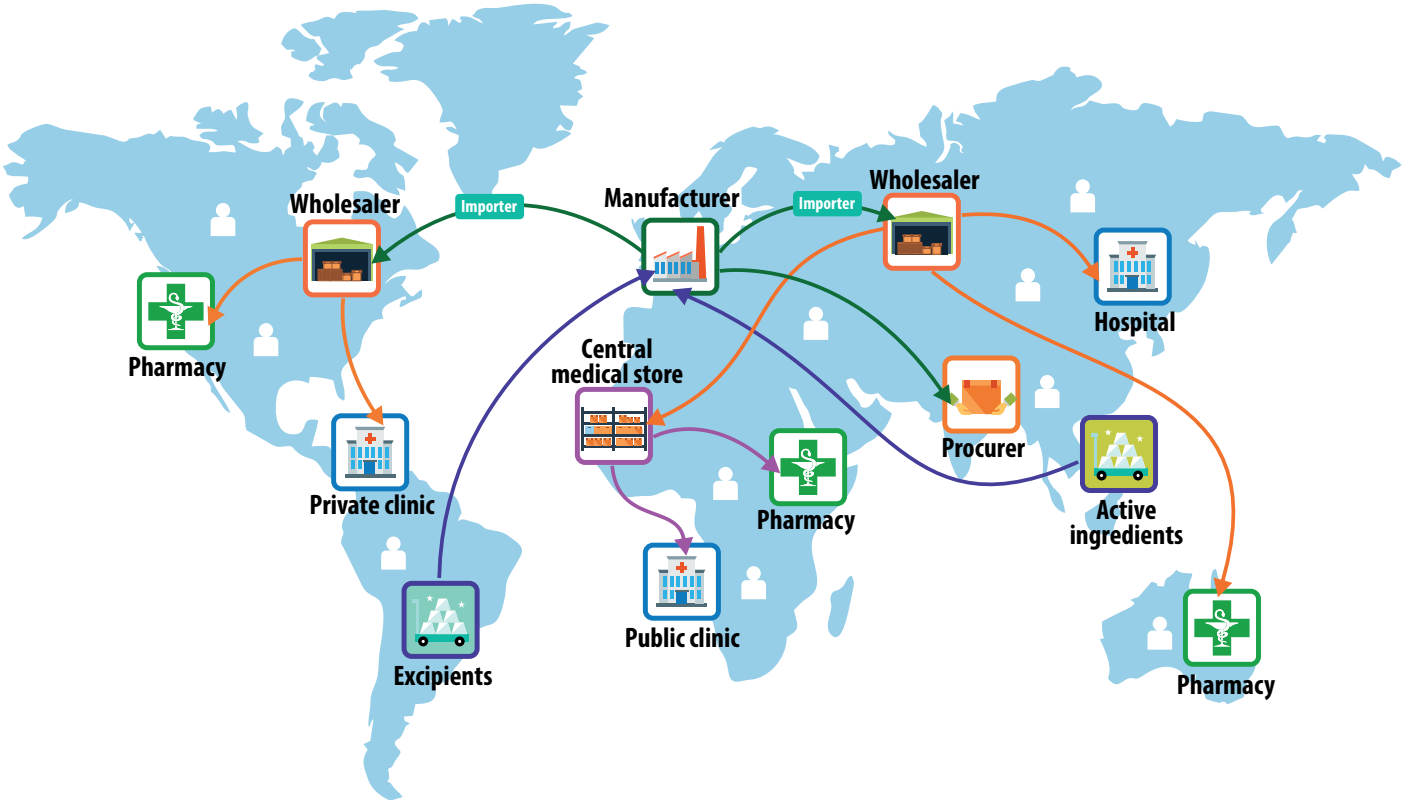
As the cough syrup case illustrates, the trade in medicines, active pharmaceutical ingredients and excipients is global. Nowadays, a tablet taken in Germany may be made in Egypt from ingredients imported from India, Brazil and Spain, packaged in foil that came from China, inserted into a box designed for the United Kingdom of Great Britain and Northern Ireland, and shipped to Liverpool by way of Dubai. A trader in the United Kingdom, taking advantage of fluctuations in the foreign exchange rate, might legally repackage the medicines with information written in German and ship it to Munich.

This extraordinary complexity, which is illustrated below in a much simplified way (Fig. 2), involves a high turnover of products passing through many hands and presents numerous opportunities for mistakes, bad practice and unethical activity.

2.4 Wasting money

While substandard and falsified medical products in the unregulated and informal marketplaces are sometimes less expensive than quality, safe and effective medicines, they cost more in the long term (*8*). Uninsured patients have to dig deep into their pockets a second time to buy effective treatment when a substandard or falsified product fails to work. These patients are often among the very poorest. Insurance companies or national health systems also have to pay twice if medical products fail to work. Further, they face the extra costs of coping with the adverse reactions and drug-resistant infections that substandard and falsified medicines and vaccines can trigger. The legitimate pharmaceutical manufacturers must bear the cost of product recalls, and they may lose out substantially if falsified products undermine consumer confidence in their products.

FIG. 2: A MEDICINE'S JOURNEY



The people that benefit most from the trade in falsified medicines are criminals. The international policing organization INTERPOL has reported that some organized criminal networks are using profits from falsified medicine operations to subsidize other clandestine activities (*9*).

The box below summarizes the consequences of substandard and falsified medical products, as detailed in the preceding chapter.

BOX 3: Key points

It is very difficult to quantify the impact of substandard and falsified medical products, for reasons discussed in section 3. However there can be no doubt that substandard and falsified medical products:

- endanger health, prolong illness and even kill;
- promote antimicrobial resistance and the spread of drug-resistant infections;
- undermine confidence in health professionals and health systems;
- create distrust about the effectiveness of vaccines and medicines;
- eat into the limited budgets of families and health systems;
- provide income to criminal networks.

Unless action is taken now to prevent, detect and respond to the further spread of these products, these factors will threaten progress towards meeting the Sustainable Development Goals.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3. UNDERSTANDING THE PROBLEM: ANALYSIS OF THE DATA

The first question most people ask about substandard and falsified medical products is: how many of them are there? It is a question that cannot be answered using information from WHO's GSMS alone. This is because the system receives reports mainly from focal points in NMRAs who have been trained to identify and report incidents. However, the absolute magnitude and overall shape of the problem can be further illuminated through deeper analysis of the 1500 reports of substandard and falsified medical products reported to WHO's surveillance and monitoring system in its first four years of operation.

Indeed the prevalence question is frustratingly difficult to answer using any available data source, for reasons outlined below. A much more detailed review of all of the available data is provided in a publication commissioned by the Member State mechanism on substandard and falsified medical products released by WHO together with this report : "*A Study on the Public Health and Socioeconomic impact of Substandard and Falsified Medical Products*".

3.1 A global issue

The WHO system receives reports from every region of the world, providing strong evidence that the problem is global.

FIG. 3: COUNTRIES IN WHICH SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS HAVE BEEN DISCOVERED AND REPORTED TO THE WHO GSMS, 2013–2017

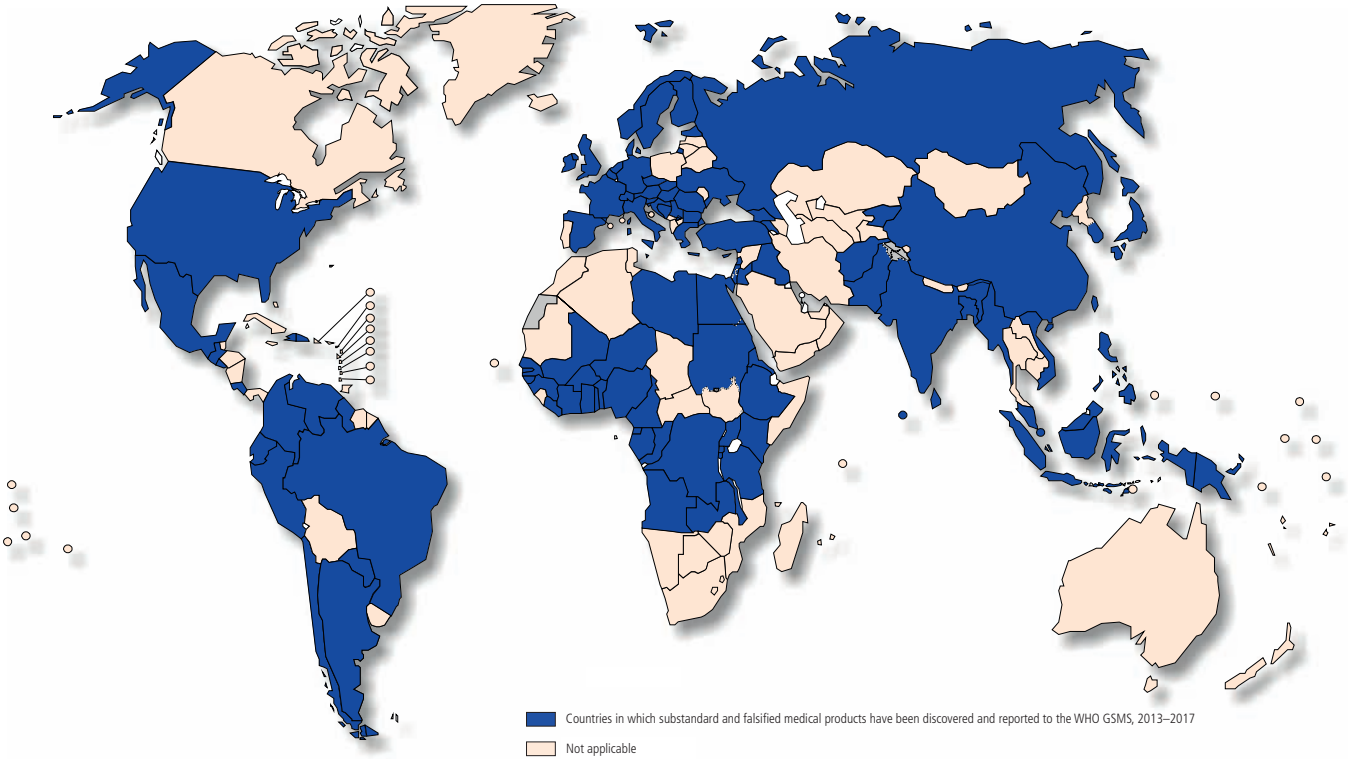


Fig. 3 maps all of the incidents recorded in WHO's substandard and falsified medical products surveillance database from 2013 to 2017.[4]

Many assume that high-income countries with strong regulatory systems can effectively exclude substandard and falsified medical products from their markets, but, as the map in Fig. 3 shows, that is not necessarily the case. Well-regulated countries usually have the resources and the networks to survey, investigate and respond internally, so unless there is a clear cross-border threat, they may be less likely than under-resourced countries to report the discovery of substandard or falsified medicines to WHO. And yet despite this, WHO's database contains reports from several countries in western Europe and North America as well as other high-income settings.

Equally the manufacture of falsified products is also a global and complex activity. Manufacturing sites linked to the clandestine production of falsified medicines and vaccines have been discovered on all continents. Sometimes production is carried out on an industrial scale at one location or it may be on a smaller and less sophisticated scale.

Often the packaging and the medicines are manufactured and printed in different countries and all of the components are shipped to a final destination where they are assembled and distributed. For example, falsified medicines originating in Asia might be packed in falsified packaging originating in Africa or the reverse. The products are sometimes concealed or smuggled and declared on the accompanying paperwork as something other than medicines. Falsified medical products are commonly shipped by air or sea, often using complex or unusual routes. Sometimes, offshore companies have been used to facilitate the sale of the falsified medicines and offshore bank accounts used to make payments and for the movement of funds.

No part of the world escapes the challenge of substandard and falsified medical products.

3.2 The more one looks, the more one finds

Can it be concluded that the countries not shaded in Fig. 3 do not face any problem with the quality of the medical products in their markets? Absolutely not. Reports of substandard and falsified medical products depend on their presence in a market. But the number of reports is also determined by who is looking out for those products, whether they know how to report them, and whether those reports are actually sent to the WHO GSMS. Since 2012, WHO staff have been training regulators, appointed by NMRAs as focal points for substandard and falsified medical products, in the use of the WHO surveillance system. Those focal points are mandated to provide, receive and share information about potentially substandard or falsified medicines with WHO, regional networks and other partners. It was expected that reporting through the platform would increase as more focal points were trained, and as national regulators became more familiar with the benefits of being able to check suspect products against a global database. Fig. 4 suggests that this is what has happened. The figure shows a clear increase in the number of products reported as more focal points have been trained.

[4] In the database, an "incident" refers to the discovery of substandard or falsified medical products at one time and place, while a "product" refers to a particular medicine, vaccine or diagnostic kit. An incident can refer to one dose of one medicine, or to a container filled with millions of doses.

FIG. 4: CUMULATIVE NUMBER OF FOCAL POINTS TRAINED, AND OF PRODUCTS REPORTED TO THE WHO SURVEILLANCE AND MONITORING SYSTEM DATABASE (FROM PILOT PHASE TO 2017)

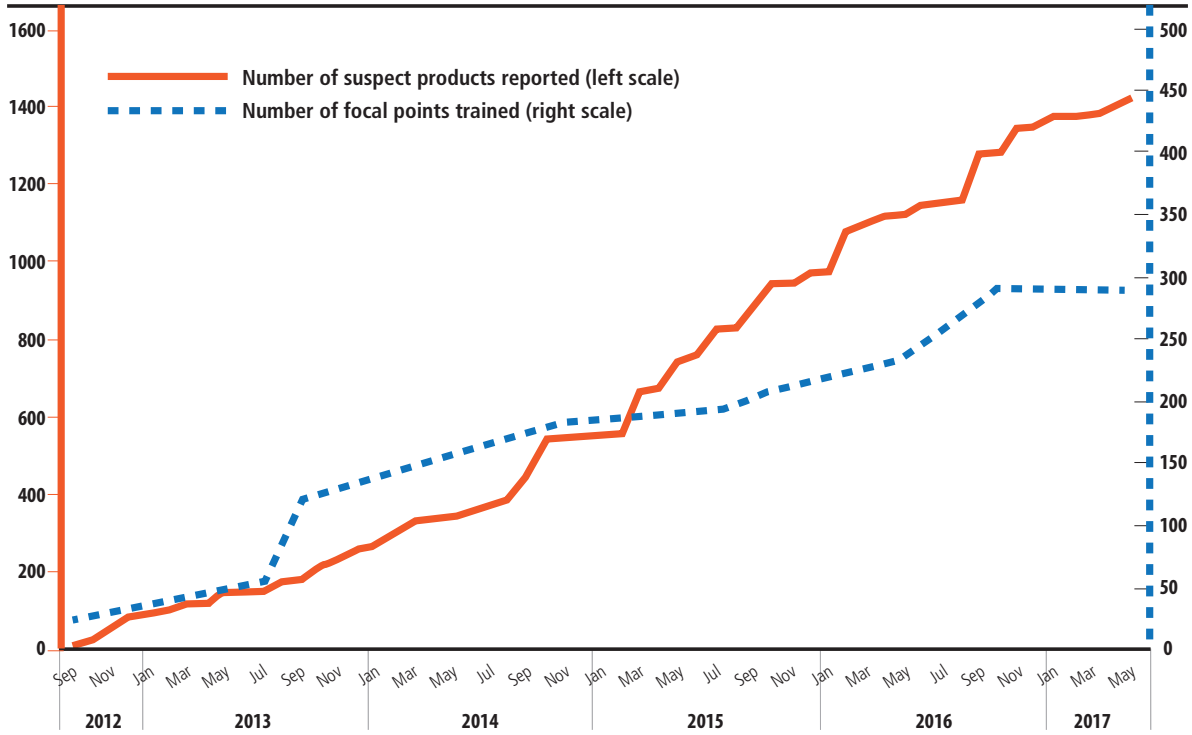
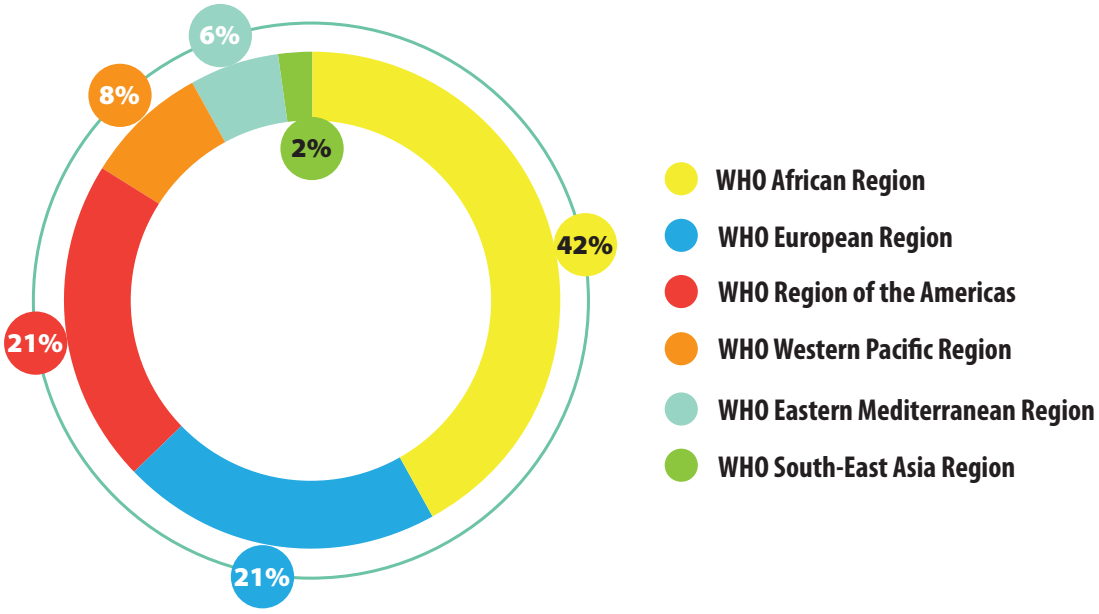


Fig. 4 underlines the value of mandating and training particular individuals to act as the pathway for information, sensitizing health care workers and others about the threats posed by products that do not meet quality standards, heightening their level of awareness, and providing avenues for reporting.

Regions that received training earlier have, broadly speaking, reported more cases. The presence of strong regional medicine quality surveillance networks, such as those in western Europe and the Americas, also contributes to higher reporting levels to the GSMS (Fig. 5).

FIG. 5: PERCENTAGE OF REPORTS FROM EACH WHO REGION TO THE GSMS (2013–2017)



Taken together, these data strongly suggest that the greater the efforts made to look for substandard and falsified medical products, the more of them are found. That leads to a second conclusion: because the system is new, the appointment of focal points was only formalized in 2017, and training is ongoing, it is highly likely that the cases now reported represent only a fraction of the problem.

3.3 From lifesaving to lifestyle products

The database reveals a third fact: substandard production and falsification affect all types of medical products. Much of the media coverage concerning "fake" medicines, particularly those purchased over the Internet, has focused on what are sometimes known as lifestyle medicines, such as slimming tablets and treatment for impotence. But over the past four years, the database has received notifications for everything from cancer medicines to contraception, from antibiotics to vaccines. Table 1 illustrates some of these. It shows the number of different products of a given type, the number of countries reporting substandard or falsified versions of such products, and the total number of reports in each category.

TABLE 1: EXAMPLES OF SUBSTANDARD AND FALSIFIED PRODUCTS REPORTED TO THE GSMS (2013–2017)

Type of product	Number of Member States reporting	Total no. of product reports	Percentage of all products reported to database [a]
Anaesthetics and painkillers	29	126	8.5
Antibiotics	46	244	16.9
Cancer medicines	19	100	6.8
Contraception and fertility treatments	19	29	2.0
Diabetes medicines	7	11	0.8
Heart medicines	22	75	5.1
HIV/hepatitis medicines	9	43	2.9
Lifestyle products [b]	37	124	8.5
Malaria medicines	26	286	19.6
Mental health medicines	19	45	3.1
Vaccines	11	29	2.0

[a] Since only selected products are reported in this table, the percentages in this column do not add up to 100%. A table showing the breakdown of all reports using the anatomical therapeutic chemical classification is provided in the Annex.

[b] So-called lifestyle products include products for cosmetic use, erectile dysfunction, body-building and dieting.

Although press coverage tends to focus on the well-known brands usually made by innovator pharmaceutical companies, the WHO surveillance database contains roughly as many examples of generic products. Those involved in the falsification of medicines are focused on profit. If a demand exists it does not matter to them if the medicine is a branded or generic version or which particular company produces the genuine version.

Again, it is important to underline that these reports do not give the full picture. The high number of malaria-related products reported to the database reflects the seriousness of the issue in this sector, certainly. But it is also influenced by the fact that the largest single procurer of malaria-related products, the Global Fund to Fight AIDS, Tuberculosis and Malaria, runs routine surveys of the quality of products in the market and reports its findings to the WHO Substandard and Falsified Medical Products Surveillance Group. The number of reports on lifestyle-related products is low relative to other data sources and estimates, in part because some national authorities may consider these products of less public health importance than

lifesaving products, so they may be less inclined to dedicate resources to investigating them, or to reporting them to WHO when they are found.

This said, the reports do draw attention to the fact that a significant number of the medical products most important for maintaining the health of people at all income levels facing many different health threats are currently being poorly produced, stored or transported, or falsified. This is underlined by Table 2, which provides data broken down by categories reflecting likely public health importance.

The WHO Model List of Essential Medicines (EML) contains the medicines considered to be the most important in meeting the needs of a health system. Products are listed for specific indications in precise dosages and formulations: the EML covers all therapeutic categories, and includes medicines, vaccines and antivenoms.

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, three different categories were developed: access, watch and reserve groups:

- ***Key access antibiotics*** are those that appear as first or second choice antibiotics in at least one entry of the WHO EML. They are the antibiotics that should be widely available, affordable and quality-assured. Selected access antibiotics may also be included in the watch group.
- ***Watch group antibiotics*** include antibiotic classes that have higher resistance potential and so are recommended as first or second choice treatments only for a specific, limited number of indications. These medicines should be prioritized as key targets of stewardship programmes and monitoring. This group includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance
- ***Reserve group antibiotics*** are those that should be treated as "last resort" options that should be accessible, but whose use should be tailored to highly specific patients and settings, when all alternatives have failed (for example, serious, life-threatening infections due to multi-drug resistant bacteria). These medicines could be protected and prioritized as key targets of national and international stewardship programmes involving monitoring and utilization reporting, to preserve their effectiveness.

TABLE 2: KEY WHO MODEL LIST OF ESSENTIAL MEDICINES (EML) ANTIBIOTICS AND ANTIMALARIALS REPORTED TO GSMS (2013–2017)

Type of medicine	Number of Member States reporting	Total no. of product reports	Percentage of all antimicrobials reported to GSMS
Key access antibiotics	36	186	30.09
Watch group antibiotics	19	38	6.14
Reserve group antibiotics	2	2	0.32
Antimalarial medicines	25	285	46.11
Any EML product – as per exact dosage and formulation	68	714	Not applicable

3.4 Low detection levels and poor reporting culture

There are a number of barriers affecting the transparency and reporting of incidents involving substandard and falsified medical products and they affect all levels of the supply chain.

A licensed manufacturer whose product is falsified by criminals has to deal with the reputational damage and loss of confidence in their own genuine medicine that may result. This may adversely affect revenues and incur costs associated with recalling products from the market – costs borne by the genuine manufacturer through no fault or actions of their own. Good corporate governance dictates that any company should immediately report such incidents to their own national competent authority, and some do. But some do not, partly for the reasons outlined above or sometimes because they are wary of unpredictable and disproportionate responses by regulatory authorities. Some countries have now passed legislation requiring the reporting of falsified medical products by manufacturers to the regulatory authorities, but better collaboration between industry and regulators on this issue is also important in dismantling this barrier.

Creating an environment where accidental manufacturing errors can be confidently reported and responded to consistently and proportionately can also reduce the risks posed by substandard medical products.

In one region, regulators receive reports from wholesalers and distributors who have been offered medicines that they consider to be suspicious. Such medicines may be offered in unusual quantities, with unusual regularity or at unusual prices. This type of reporting is rare; too often a lack of due diligence from where medicines are being sourced in the supply chain has resulted in substandard and falsified versions reaching patients through hospitals, clinics and pharmacies – the locations where patients should have the highest degree of confidence that the medicines are safe.

Health care professionals are a source of accurate and often reliable reports, but again a number of factors may also lead to a culture of non-reporting. Barriers identified include a lack of awareness, either no system or no method for reporting, overcomplicated reporting systems, low response from regulatory authorities or a lack of feedback. These issues are addressed later in this report. But, worryingly, health care professionals sometimes cite a fear of reprisals either from their managers or those engaged in distributing substandard and falsified medical products. A fear of corruption and a concern that they may be open to prosecution or civil actions themselves may discourage health care professionals from reporting suspect products. These are more difficult issues to confront, but failure to address them will cause the problem of underreporting to remain.

Purveyors of falsified products often invest heavily in perfecting the look of their packaging, so, from the point of view of a consumer or a product distributor (e.g. a pharmacist), falsified products can be very hard to identify. They are more likely to come to the attention of health services because they do not have the expected therapeutic effect.

3.4.1 Limited additional data from other sources

The WHO GSMS provides some insights into the size and scope of the trade in medical products that are falsified, poorly made or degraded, but it is impossible to determine exactly how many are in the market.

No other existing source of information is likely to provide a firm answer. As already discussed, the pharmaceutical market is a trillion-dollar, hyperglobalized business. In any given year billions of doses of medicines in hundreds of thousands of formulations are sold around the world, in countries that have different standards and regulations. That is before even considering all the diagnostic kits and other medical products. Falsified medical products are usually made and packaged by criminals, who work hard to remain undetected. Some are low-investment, low-tech operations working out of homes and garages. However, there is also plenty of evidence of industrial-scale production – see, for example, section 3.4.1, which relates how Angolan customs officials seized 33 million doses of fake antimalarials hidden in a consignment of stereo speakers on a ship from China. Many of those engaged in the manufacture of substandard and falsified medical products are very

sophisticated; they quickly begin to copy holograms and other authentication devices used by legitimate manufacturers to make falsification harder. So detecting falsified medicines before they get to the patient is extremely difficult.

Scientifically speaking, the most appropriate way of estimating the proportion of substandard and falsified medical products would be to take a random sample from a representative cross-section of outlets. The samples would then be tested for active ingredients to see if they dissolve or otherwise distribute themselves correctly so that the active pharmaceutical ingredient gets to where it needs to be in the body of the patient – a characteristic known as bioavailability. Field surveys with random sample collection have only ever been done for a small handful of medicines in limited geographical areas – it is too time-consuming and expensive to do on a large scale. Until recently, very few research funders had invested substantially in field-based studies tracking the prevalence of substandard and falsified medical products.

Field surveys find high prevalence in some markets

Most of the surveys that have been carried out have focused on medicines and/or geographical areas where researchers expected to find a problem. In the mid-2000s, fears about growing resistance to artemisinin, once the last remaining universally effective antimalarial, focused attention on malaria medicines, so those are widely studied, especially in Africa and south-east Asia. Academic researchers have also looked at antibiotics in several countries, most of them low- and middle-income. A new review of all of the existing academic studies, published in conjunction with this report, estimates that in these low- and middle-income countries, about one medicine in 10 does not meet acceptable quality standards. Some are clearly falsified – they contain no active ingredient at all, and the packaging gives names and addresses of manufacturers that do not exist. Many others have less than the advertised amount of active ingredient and it is often extremely difficult to tell if that is deliberate (which would mean the medicines were falsified) or accidental (the result of a production error or inadequate packaging and storage, leading to degradation). These difficulties can be exacerbated if researchers and the manufacturers of the legitimate product do not work together during the studies.

The Internet gateway

Few randomized surveys of medicine quality have been carried out in high-income countries. This is partly because researchers may view the risk as lower, and that a random sample would yield very few substandard or falsified products. But, as Fig. 3 makes clear, "no data" does not mean that there is no problem. Risk-based surveillance, which focuses detection resources on the products and supply channels most at risk for falsification, indicates that in some high-income countries, medical products bought over the Internet from illegal or unauthorized websites, social media platforms or smartphone applications frequently fail to meet quality standards (*10*).

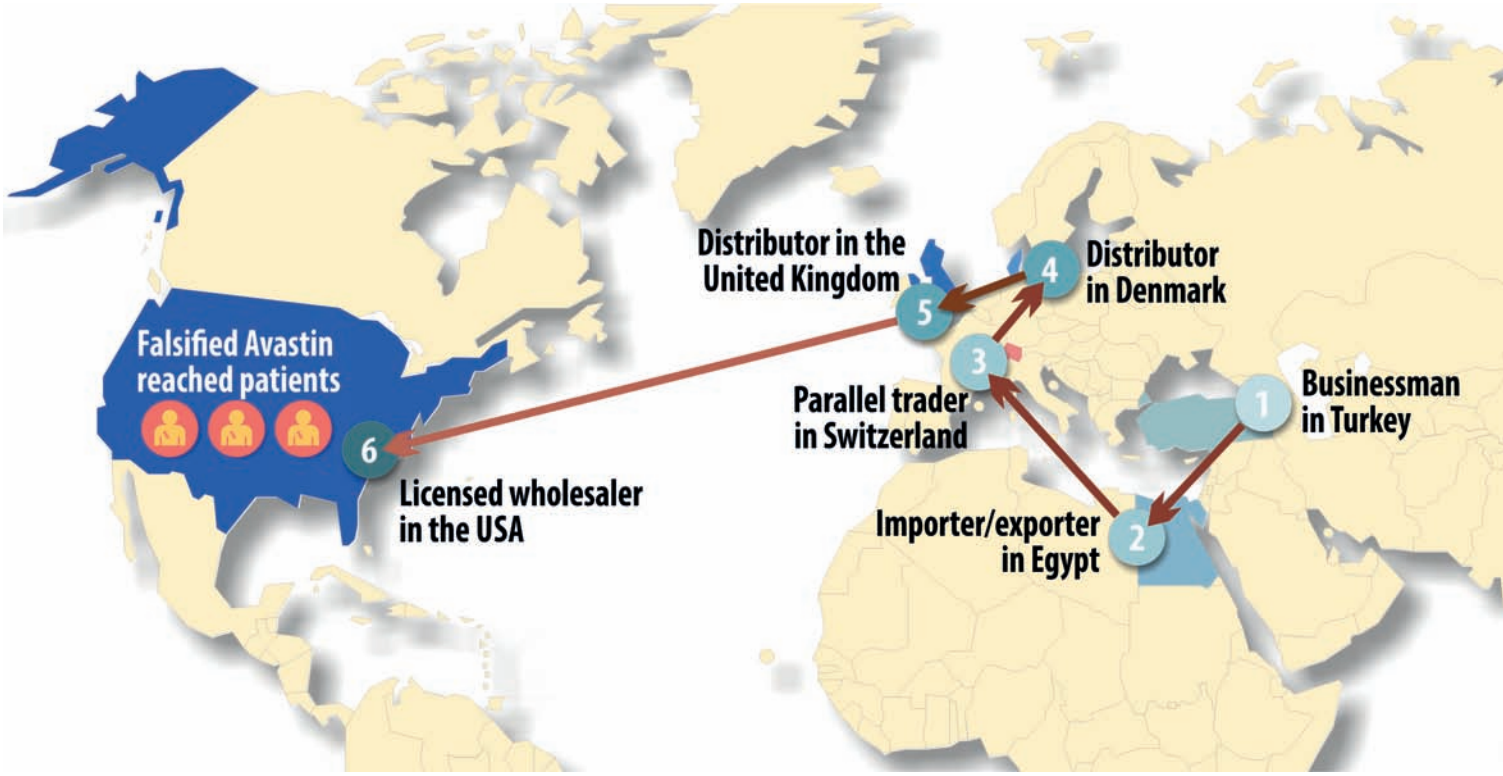
Those products include lifesaving as well as lifestyle medicines; the e-commerce market for both is growing. Online pharmacies are especially popular with consumers in high-income countries – nationally representative surveys in the United States of America, for example, show that the number of people buying medicines online has more than quadrupled in less than a decade. Between 19 and 26 million people in the United States alone now buy medicines over the Internet (*10–12*). Buying from the Internet is increasingly popular in middle-income countries, too. Besides being convenient, buying medical products over the Internet provides anonymity; that is often attractive to people wanting products relating to impotence or to treat stigmatized conditions.

The inexorable growth in online sales provides criminals with a relatively easy entry point into even the best regulated markets. Authorities around the world are working to tackle this new challenge, but it is universally recognized to be a difficult task. National medicines regulators regularly collaborate to tackle the issue of poor quality medicines supplied online. For example, in 2016, 103 countries were involved in the annual operation Pangea (coordinated by INTERPOL), now in its tenth year, which led to the suspension of 4932 Internet pharmacies and nearly 400 arrests (*13*). This operation focuses on disrupting the infrastructure required by websites illegally supplying medical products, through working with domain name registrars, payment providers and courier companies. This operation provides a platform for delivering clear and coordinated health messages to consumers about the increased risks of obtaining

medicines from unregulated websites, through the widespread media attention that it attracts.

Regulating the supply of medicines and investigating the online supply of substandard and falsified medical products is complex, often involving several countries. This can lead to jurisdictional complexities and the requirement of evidence from multiple countries. As an example, Fig. 6 illustrates the countries involved in the Avastin case mentioned in section 4.1.1.

FIG. 6: MAPPING THE SUPPLY CHAIN OF FALSIFIED AVASTIN



WHO and its partners are working to develop methods that will allow for more accurate quantification of the number of substandard and falsified medical products. However, there is already enough evidence to show that the problem is substantial, it is global, and it affects many types of lifesaving products. It can be argued that this is more than enough to justify, and indeed demand, a substantial effort from all stakeholders to prevent, detect and respond to the threat posed by these products.

3.5 Classifying reported products

Medical products reported to the GSMS are all classified based on the information provided by the reporting country, laboratories and sometimes the manufacturer. This classification is made according to the definitions of substandard, falsified and unregistered medical products agreed by the Member State mechanism and approved by the seventieth World Health Assembly (Table 3). The purpose is to enable more accurate analysis and comparison of data.

WHO will attempt to obtain as much information as possible from the reporting country and any other reliable and available sources in order to make an accurate classification.

TABLE 3: CLASSIFICATION OF REPORTS RECEIVED BY THE GSMS

Classification type	Criteria
Confirmed that the medical product is substandard, falsified or unregistered	Verification by the following parties: ▪ The stated manufacturer, or the manufacturing authorization holder, that either/or any of the points below do not correspond to the stated manufacturer's records: – laboratory analysis of the medical product, and/or – examination of primary and/or secondary packaging, and/or – batch numbers and/or expiry dates and/or manufacturing dates. ▪ A government quality control laboratory confirms that the product does not meet specifications.
Highly probable that the medical product is substandard, falsified or unregistered	▪ The product has failed field screening examination, and/or ▪ Samples are unavailable for laboratory analysis and/or ▪ Photographic evidence suggests the product is substandard, falsified or unregistered.
Insufficient information	▪ There is an absence of further confirmatory information available to WHO or available information is deemed unreliable.

The relatively small number of confirmed substandard medical products contained in the database is probably the result of lower detection rates as well as greater underreporting and the complexity of investigation required. Substandard medical products are usually properly packaged, often bought through trusted supply chains, and often also contain a percentage of the correct active ingredient. This means they may have at least some effect on the patient, so neither health workers nor patients quickly suspect that the medicine is not working properly.

The box below summarizes the analysis of the GSMS data on substandard and falsified medical products, as detailed in the preceding chapter.

BOX 4: Prevalence: a summary

It is not currently possible to assess the absolute number of substandard and falsified medical products in specific markets or worldwide. However, existing data show that:

- substandard and falsified medical products exist in every region;
- the more one looks, the more one finds;
- the problem affects a wide range of products, including vaccines, common antibiotics, antimalarials, cancer medicines and other lifesaving medical products;
- those falsifying medical products target both generic and innovator products.

4. SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS: THE CAUSES

Better information on the number, types and distribution of suspect substandard and falsified medical products would certainly be helpful, but the most important first step towards actually reducing the problem is to understand why it occurs. That means understanding both motivations and opportunities.

Falsification of products that are believed to cure illness is nearly as old as commerce itself. In 1500 BC, Queen Hatshepsut of Egypt hired a team to go out hunting for genuine medicinal plants because the market was flooded with worthless fakes. In the eighteenth century, when malaria was still endemic in Europe, the continent was inundated with fake and poor quality cinchona bark, used to treat fevers. A British doctor, William Saunders, pinpointed both the reason for the falsification and its consequences in a pamphlet published in 1783: "There is some danger, from the avarice of dealers, of [the bark] being adulterated … a circumstance which may bring it into disrepute" (*14*).

"The avarice of dealers" – in more modern terms, greed – continues to be a driver of the trade in falsified medical products, just as "disrepute" – the undermining of public confidence in medicines – is still one of its consequences. But the desire to make a quick profit is just one of a complex web of factors that lead to the production, distribution and consumption of substandard and falsified medical products.

As noted in Chapter 2, there are now more of these products, in part because the global demand for medicines, vaccines and diagnostic kits has grown so rapidly in recent years. The growing market has created new opportunities for unscrupulous traders, businesses, and criminals. By analysing the database of cases reported to WHO as a whole it is possible to begin to identify patterns – clusters of factors and trends that allow the makers and sellers of substandard and falsified products to thrive.

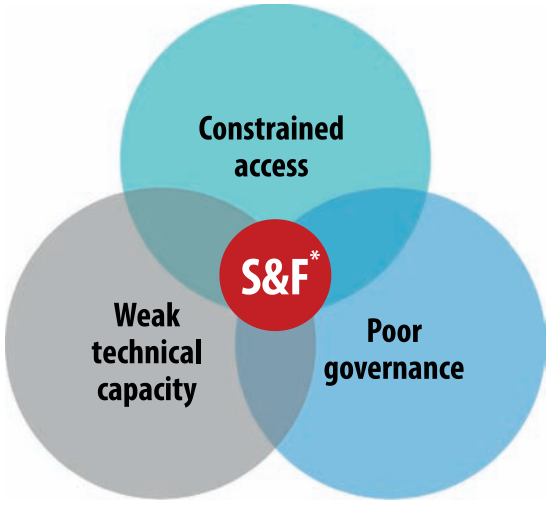
Like any other commerce, the trade in substandard and falsified medical products depends on profit margins. It does best where demand is high, and where there is a shortage of supply; indeed even very low-cost products are attractive as long as the potential sales volume is high enough. The trade is driven by an unsavoury combination of the ill-informed, the careless, the unprincipled and the criminal, so it thrives in places where the technical capacity is poor and the risk of detection is low.

In short, substandard and falsified medical products are most likely to be found at the intersection where:

- Access to affordable, quality, safe and effective medical products is constrained.
- Standards of governance are low, from poor ethical practices in health care facilities and medicine outlets, through to corruption in both the public and private sectors.
- The tools and technical capacity to ensure good practices in manufacturing, quality control and distribution are limited.

Fig. 7 represents this graphically.

FIG. 7: CONTRIBUTORY FACTORS TO THE EMERGENCE TO SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS



*S&F : substandard and falsified medical products

Very broadly speaking, **substandard** medical products reach patients when the tools and technical capacity to enforce quality standards in manufacturing and the supply chain are limited. Technical limitations also affect **falsified** products, but their circulation in the market is further promoted by corruption and other shortcomings of regulation and governance, including unethical practice by wholesalers, distributors, retailers and health care workers. However, a high proportion of cases so far reported to WHO occur where these problems overlap with constrained access.

4.1 Constrained access to affordable, safe and quality medical products

Medical products that are falsified or poorly made find their easiest access to the market when they fill a vacuum. That vacuum often arises when people need or want medicines that they cannot obtain or afford. Although the brunt of this restricted access is borne by individuals, the shortages often arise further up the supply chain. Pharmacies, hospitals and other care providers often cannot secure what their patients need. Sometimes, shortages arise nationwide, for example because a necessary product is too expensive for the national health system, or because an unexpected disease outbreak has caused demand to outstrip the global production capacity of known suppliers. In all of those cases, people and institutions do things they would not normally do, for example order a batch of medical supplies from an unknown, untrusted and unlicensed source.

4.1.1 Affordability

The price of a medical product is an important consideration for many patients and their families, especially if it is not sufficiently covered by insurance or by a national health system, and if people have to pay for it out of their own pockets. If a good quality medicine from a known supplier is too expensive, people may try a cheaper one, bought from an unlicensed supplier, in a street market (Fig. 8) or over the Internet. Cost pressures are also felt throughout the production and supply chain, as well as in the insurance industry. Some businesspeople at all levels cut corners in an attempt to maximize the profit margins they earn, with consequences that can undermine the quality of the medical products that reach patients.

FIG. 8: MEDICINES SOLD BY STREET SELLERS IN WEST AFRICA

Changes in insurance policies brought falsified cancer medicines to the market

Avastin, a trademarked brand of the cancer medicine bevacizumab was widely used in the United States to treat many types of cancer, including advanced breast cancer, at a cost of around US$ 2400 per injection. In November 2011, following a review of new clinical trials that showed no real benefit for breast cancer patients, the United States medicine regulator (US FDA) decided that the manufacturer should no longer sell it for that use. Several health insurance companies changed their policies to match, saying they would not cover the cost of the medicine for new users. But some women and their doctors still wanted to use it (*15–17*).

Three months after the change in policy, the US FDA announced that at least 19 medical practitioners in the United States had bought falsified Avastin from a Montana-based distributor who (according to a court indictment filed in 2015), was linked with an Internet pharmacy purporting to be based in Canada (*18*). The distributor was reported to be offering the sophisticated injectable medicine under its Turkish brand name Altuzan for US$ 1900 per dose, US$ 500 less than its normal price in the US market at the time. When the US FDA tested suspect vials of the medicine, they found that it contained no bevacizumab.

Unravelling the supply chain proved difficult. The US distributors had acquired the medicine via the Internet-based pharmacy from a subsidiary wholesaler based in the United Kingdom. The British dealer had bought it from a company in Denmark, according to regulators. The Danish company, in turn, had acquired it from a Swiss company, who were supplied by an Egyptian businessman. The Egyptian told the Reuters news agency that he had himself bought the medicines (thinking they were the genuine article, made in Turkey) from a Syrian dealer, who signed a hand-written sourcing document with his thumb-print because he could not write (Fig. 6) (*19,20*).

The case demonstrates just how complex the global pharmaceutical trade has become. The more frequently legitimate medicines change hands, and the more national borders they cross, the harder it is for national regulators to ensure that no falsified or substandard medical products penetrate the supply chain.

Much of the vast trade in legitimate medical products occurs because of price differentials, both in the cost of production and in the cost of medicines on the market. Pharmaceutical manufacturers in high-income countries often acquire their active ingredients from factories in countries with lower production costs, and they sometimes contract production of finished product out to lower-cost countries too (*21*). Arbitrage, which takes advantage of price differences between markets, is especially common in the European Union. There, trade rules allow for the free flow of goods between countries but health care financing regimes differ, so that medical products are more expensive in some nations than others. Together with fluctuations in exchange rates between the euro and other European Union currencies, this creates opportunities for traders to buy goods in lower-priced markets, sometimes legally repackaging them for resale in higher-priced markets. This practice, known as parallel trade, is perfectly legal. But it complicates regulation, including by legitimizing placing stickers or repackaging over original packaging, printed with information in another language. This can make falsified products harder to detect. Parallel trade can also contribute to shortages in lower-priced markets. At the time of the bevacizumab case described above, the Parliament of the United Kingdom was taking evidence about shortages caused by the export of medicines intended for the United Kingdom market to other countries where they sold for higher prices (*22*).

FIG. 9: FALSIFIED AVASTIN THAT PENETRATED THE SUPPLY CHAIN AND REACHED PATIENTS

©US Food and Drug Administration

The high cost of hepatitis C treatment

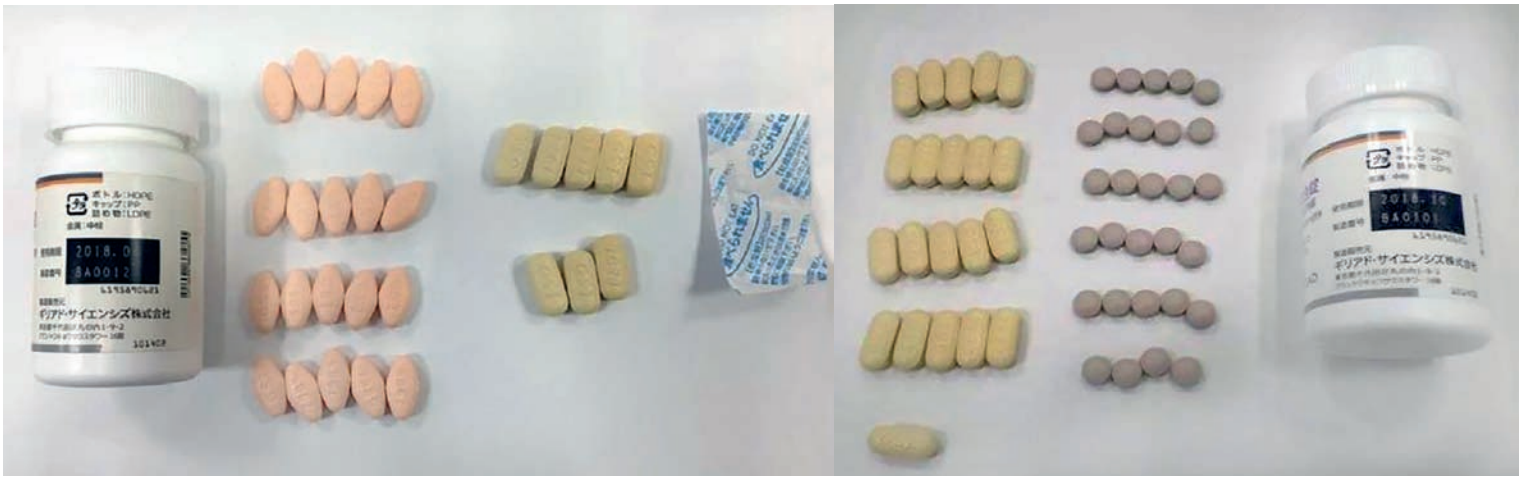
Hepatitis C can lead to cirrhosis or cancer of the liver, but in general people live with the infection for many years before that happens. In late 2013, sofosbuvir was approved for the treatment of hepatitis C under the brand name Sovaldi. Studies showed it cured over 90% of the patients who took it in conjunction with two other medicines: ribavirin and interferon. When it was first marketed in the USA, the three medicines cost approximately US$ 95 000 for the 12-week course that can cure a patient (*23*). Months later, another product with the trade name Harvoni, containing sofosbuvir and ledipasvir, and made by the same company, came on-stream: Harvoni was just as expensive as the three-drug regimen, but the single medicine was easier to take, and was perceived to have fewer side-effects.

A study in September 2016 found that the actual net prices charged (after discounts to bulk buyers) were somewhat lower than the list price – US$ 50 400 for a 12-week course of Harvoni in the USA, and US$ 44 500 for Sovaldi. In Japan, Harvoni was even more expensive, at US$ 55 500 per course, compared with US$ 43 000 for Sovaldi. But in 2016, Japan was treating more of its hepatitis C-infected population than any other country, and demand for the medicine perceived to have fewer side-effects was high (*24*). For criminals, it was easy to spot the opportunity in that situation: by substituting one medicine for the other, a profit of more than US$ 10 000 could be made per patient.

That opportunity was recognized by those who supplied a pharmacy in Tokyo in January 2017. They did not stop at taking a (genuine) Harvoni bottle and filling it with Sovaldi tablets (Fig. 10). They included vitamin tablets as well – tablets that were different shapes and colours, and that of course would do nothing at all to cure a potentially fatal illness. This is obviously not a good business model even for criminals – it was inevitable that this extraordinarily crude attempt at falsification would be detected speedily. But the high price of some medicines means that a large sum of money can be made very quickly by deceiving a small number of consumers.

This is not a problem that is confined to a single market. Falsified hepatitis C medicines – both innovator and generic versions – have also been reported to WHO from other high- and middle-income countries around the world.

FIG. 10: FALSIFIED HARVONI DISPENSED IN JAPANESE PHARMACIES



©Ministry of Health, Labour and Welfare, Japan/Gilead Sciences Inc.

Cost pressures throughout the supply chain

As the Avastin case shows, health care professionals ordered medicines from suppliers who provided a conduit to medicines acquired in a cheaper market. In many other countries, the price that a pharmacy can charge a patient for a medicine (or the amount that insurers will reimburse) is fixed. Profit margins depend on how much the pharmacist pays to obtain the medicine. The promise of low prices sometimes overwhelms common sense so much that buyers ignore the need to check the legitimacy of suppliers. Legitimate suppliers face the same price pressures and are always looking for cost-savings themselves. This creates opportunities for substandard and falsified medical products to enter the supply chain at many different points.

In Ghana, for example, drug inspectors found tablets masquerading as antimalarial medicines in a rural dispensary near the border with Côte d'Ivoire. Laboratory tests showed they contained less than 2% of the expected active ingredients – perhaps enough to deceive the most basic testing kits, which change colour if they come into contact with the active ingredient, but certainly not enough to save the life of a sick child. Investigating authorities found that the dispensary had not stepped outside the regular supply chain – they bought the medicines from a licensed wholesaler that they had done business with many times. That wholesaler, however, had not followed all the rules having bought the falsified medicines at a discounted price from a travelling salesman, who was selling the product cheaply from the back of a truck. The wholesaler apparently did not ask too many questions about the legitimacy of the product – they accepted the consignment without any paperwork, so the supplier could not be traced.

Pharmacists in some African countries have declared that in order to compete with the illegal street markets and hawkers of medicines they are compelled to source their products from the cheapest but not necessarily the safest suppliers in order to keep their business afloat.

Criminals look for market opportunities

In the Avastin case, changes in insurance policies created an opening which was filled with falsified medicines sold below list price. Unscrupulous suppliers also stepped in when a disease outbreak boosted demand for the meningitis C vaccine in Niger unexpectedly (section 4.1.2), and when conflict disrupted supply chains in the Middle East (section 4.1.2).

Global campaigns that aim to deploy medical products on a huge scale in the hope of eliminating a disease from a particular region, or even eradicating it from the world entirely, can also signal lucrative market opportunities to those who are engaged in falsifying medical products. Huge investments in malaria elimination efforts have slashed transmission and deaths in recent years. But they have also provided an opportunity for criminals to push falsified antimalarials into the market (as with the cases on pages 29 and 30).

New entrants to the complex world of medical procurement sometimes provide easy prey for those selling falsified products, as can people who are buying medications with which they may not be very familiar, such as treatment for rare or emerging diseases, or vaccines against diseases that are not endemic. The procurement of yellow fever vaccines in Bangladesh discussed on page 33 is an example of the latter.

4.1.2 Availability

High prices are not the only reason that people have difficulty obtaining the medical products they need. This section provides examples of many cases in which necessary medicines are simply not available. The reasons for the shortages include poor infrastructure, war, disasters or geographical isolation, all of which disrupt distribution. Sometimes, stocks have run out because of bad planning, theft or mishaps higher up the supply chain. In other cases, medicines just cannot be manufactured fast enough. When a shortage of quality medicines, vaccines or diagnostic kits occurs, other, less reliable products often quickly flow in to fill the gap.

Conflict and emergencies increase demand, while reducing supply

Conflict, which often goes hand in hand with already fragile administrative structures, disrupts the regular health systems that aim to prevent illness and treat those in need. It also displaces people, and injures them. The same is often true of emergencies created by natural disasters, such as earthquakes, hurricanes or catastrophic flooding. All these emergencies increase the need for health services and the medicines that underpin them, while at the same time reducing the likelihood that those services and medical products are available.

Kandahar, in Afghanistan, has had to deal with such a constellation of fragility. In April 2014, the city was tense ahead of presidential elections that some feared could tip the country back into civil war (*25*). A large hospital in the city, operated with the support of an international agency, was running low on ephedrine, a stimulant of the central nervous system used to keep blood pressure constant in trauma surgery and during other operations. Killings and suicide bombings had recently resumed in the city, and surgeons knew they needed the medicine in stock in case violence spread more widely following the elections. Stock management was, however, complicated by restrictions on import and export of ephedrine, which is also used as a precursor chemical in the illegal manufacture of meta-amphetamines. In order to avoid bureaucracy, many local suppliers import the medicine without all the proper clearances.

From one of these wholesalers, the hospital bought ephedrine advertised as having been manufactured by Bayer in the United States. After using it for a month, doctors began to worry; unusual numbers of their patients were suffering from hypertension. They stopped using the ephedrine, and, with the help of WHO, sent photos of the product to Bayer. They also kept samples, but there is no laboratory qualified to perform quality testing of ephedrine in Afghanistan, and the hospital was unable to send the samples to a foreign laboratory because of the strict export controls on the substance. On the strength of the photos alone, Bayer confirmed that the packaging did not match that of their genuine product.

The international agency quickly sourced an emergency supply of genuine ephedrine overseas to fill the gap before regular supply chains could be re-established. Afghan customs authorities held up the shipment, saying it could not be released until the previous (falsified) stock had been used up. Although the situation was eventually resolved, the hospital was without a quality-controlled supply of this important medicine for a full four months.

Conflicts and disasters create openings for substandard medical products because they disrupt production and undermine capacity to store and transport those products correctly. This incident highlights how political instability and conflict also create openings for falsified medicines. It also shows that rules and regulations designed to prevent other ills, such as the trade in illegal recreational drugs, can have the unintended effect of undermining access to good quality medicines. Health authorities have to collaborate closely with agencies in charge of customs, border control and the judicial system if they want to avoid such perverse outcomes. That collaboration can be especially difficult to achieve where governments are unstable.

Theft empties the shelves of medicine stockrooms

It is all too common to read about shortages of medicines in public hospitals and clinics, especially in lower income countries. One of the reasons for this is that medical products intended for distribution at reasonable cost in public and charitable facilities are diverted to other destinations. In this context, "diverted" means stolen. Medicines can be hijacked in transit; they are also sometimes stolen from the stockroom of the facility for which they were intended. Such thefts are usually driven by greed. However, some health workers surviving on desperately low salaries and who sometimes do not get paid for months at a time regard the diversion of medicines as a fair way of surviving. As one health care worker noted in conversation with a WHO employee: "Medicines are as good as money."

When the shelves of a hospital dispensary are empty, patients are forced to look for medicines elsewhere – sometimes from a street vendor, sometimes in the vicinity of a hospital. That can be dangerous, even fatal. The WHO database contains reports from at

least two countries of cases in which hospital staff sent parents to buy medicine for their children elsewhere because the hospital dispensary was out of stock. After the parents appeared with the medicines or vaccines, nurses administered them to the children. In both cases, the children subsequently died. Although investigations of the suspect products proved inconclusive, the cases certainly raise concerns about the knock-on effect of empty dispensaries.

To discourage such thefts, the manager of one health facility in Africa reported sleeping in the medicines stockroom for a period after new deliveries of medicines arrive. Such measures will not help, however, when the theft occurs further up the supply chain. This was the case in a complex incident in east Africa, which came to light after a patient complained that the antiretroviral tablets they had received free of charge from a nongovernmental organization (NGO) to control their HIV infection were mouldy. Checks by the Indian company that made the generic medicine showed that the tablets were genuine, but the packaging was not. It turned out that the medicine had been procured from India by an American organization, which asked that it be shipped to a foundation in east Africa for free distribution to patients. The foundation repackaged the antiretrovirals with falsified expiry dates, and diverted them for sale through another string of companies. One of these companies resold the medicines to NGOs, which gave them to patients free of charge.

Such problems are by no means confined to low- or middle-income countries. Italy's NMRA, for example, has reported successive waves of medicine thefts from hospitals and from trucks delivering to hospitals. The thieves target high value medicines such as those used to treat cancer (*26*).

Mishaps in planning can lead to shortages

The ability to accurately predict demand for different medical products is one hallmark of a strong health system. In wealthy countries, surveillance and service use data going back many years allow health authorities (and even individual hospitals) to make accurate estimates of what their patients will need in any given year. The task is easiest in countries where most illnesses are chronic and unexpected disease outbreaks uncommon.

Lower income countries are less likely to have such a wealth of data, or the skilled staff needed to make accurate forecasts, especially at the local level. In some countries, national-level authorities do the forecasting; on the basis of that predicted need, central medical stores are expected to deliver medicines to districts according to a regular schedule, usually quarterly. Restrictions in supplies at the national level can mean that in practice, regions do not always get what they need. Parallel centralized planning and distribution services are sometimes also maintained by disease-specific programmes and other specialized procurement and funding agencies.

These systems relieve local officials of the need to do all the planning and ordering, and where they work well, they make stock management more predictable. But they do have a downside. Predictable deliveries of significant quantities of medicines can attract thieves. And if supplies are stolen, or if they run out because deliveries fell short or demand turned out to be higher than predicted, there is no easy way of getting back-up supplies before the next scheduled delivery. That means stockouts, and as shown above, stockouts of affordable quality products provide an entry point for substandard and falsified products.

Many countries face another challenge to precise planning: unexpected disease outbreaks and emergencies. Although institutions working to promote health globally and to build system resilience have tried to develop products and systems that fill the gap, they cannot always cope when local conditions change unexpectedly.

One recent example comes from the "meningitis belt", which stretches the breadth of Africa, just south of the Sahara. Every year, from December to June, this area is prone to outbreaks of several types of bacterial meningitis. The disease often causes death, or leaves survivors with severe neurological deficit, which can affect movement and speech. Vaccines to prevent meningitis fall into two broad groups: older polysaccharide vaccines, and more advanced conjugate vaccines that provide longer-lasting protection but cost up to seven times more than their polysaccharide equivalents (*27*).

For several decades, *Neisseria meningitidis* type A was the bacteria most commonly responsible for meningitis outbreaks. In 2010, WHO and other partners began to support the widespread provision of a conjugate vaccine against that pathogen across Africa; as a result, meningitis cases caused by type A bacteria have plummeted by 57% (*28*).

In 2015, Niger and neighbouring Nigeria experienced unusually large outbreaks caused by a different variant of the bacteria: *Neisseria meningitidis* type C. The international mechanism that stockpiles vaccines to respond to outbreaks shipped available supplies to the two nations. But, because meningitis C is more rarely seen in Africa, there was not enough vaccine in stock to meet demand.

Procurement reports mention that production constraints, some exacerbated by the switch to manufacture of conjugate vaccines for meningitis A, limited the capacity of regular suppliers to rapidly increase output. In the end, the United Nations Children's Fund (UNICEF), which sources vaccines for the stockpile, had to buy products that had not been through WHO's rigorous prequalification procedure, which is designed to ensure that the best manufacturing standards are observed (*27–29*). Although Niger received 200 000 doses of conjugate vaccine and almost a million doses of polysaccharide vaccine against meningitis C from the stockpile, there was still a gap if the outbreak was to be controlled through vaccination. The government and pharmacies of land-locked Niger turned to wholesalers in neighbouring countries to fill that gap.

A month into the outbreak, a health care worker at an NGO was taking a vaccine out of the fridge when she noticed that the ink around the expiry date appeared smudged (Fig. 11). Having been sensitized by the government's designated focal point on substandard and falsified medical products to some of the techniques used by falsifiers, she reported her suspicions about two products to national regulators. They in turn alerted both the manufacturers and WHO. The manufacturers could tell from photographs that both products were falsified. Laboratory analysis of one of the products identified just two of four expected antigens in the product, although testing was limited because the laboratory only received a small amount of the suspect vaccine. The vials of this product appeared to have been refilled and relabelled. As for the other product, the vials were of a size that had been discontinued many years earlier and no samples were available for analysis.

In the end, 8580 cases of meningitis C were reported in Niger in 2015 and nearly 600 people died (30). There is no way of knowing how many of those cases might have been averted if every vaccination administered had been with a quality-assured product.

Two years later, in April 2017, Niger experienced another outbreak of meningitis C. The vaccine supply constraints have not yet been resolved – the international stockpile still carries vaccine that is not WHO-prequalified to top up its stocks (*29*). When Niger requested 340 000 doses of vaccine to respond to the new outbreak, the stockpile mechanism supplied the product, but another request later that month was only partly fulfilled (*29*).

Once again, falsified vaccines found their entry point. In May 2017, a pharmacist in the Niger capital Niamey received an unexpected consignment of vaccines from their regular wholesaler in neighbouring Burkina Faso. Remembering the falsified vaccine scandal two years previously, the pharmacist contacted the Brazilian manufacturer listed on the packaging. Although the manufacturer exists, they do not make this specific version of meningitis vaccine; the manufacturer therefore alerted regulators in Brazil, who in turn requested that the manufacturer contact the WHO surveillance team. WHO coordinated with the health authorities in Niger, who asked for help investigating the case. Early indications suggest that this new case involved far more than just extending the expiry dates on the labels of formerly genuine vials. Expertly produced labels and newly printed cartons bearing seemingly plausible but fictitious product information suggest that the falsification of meningitis C vaccine has shifted from being a cottage industry to a more industrial scale (Fig. 12).

Unless constraints on the supply of affordable, quality vaccines against meningitis C are resolved, it seems likely that such incidents will recur.

FIG 11: VIALS OF MENINGITIS VACCINE FOUND IN NIGER IN 2015 HAD THEIR EXPIRY DATE MANUALLY EXTENDED BY TWO YEARS

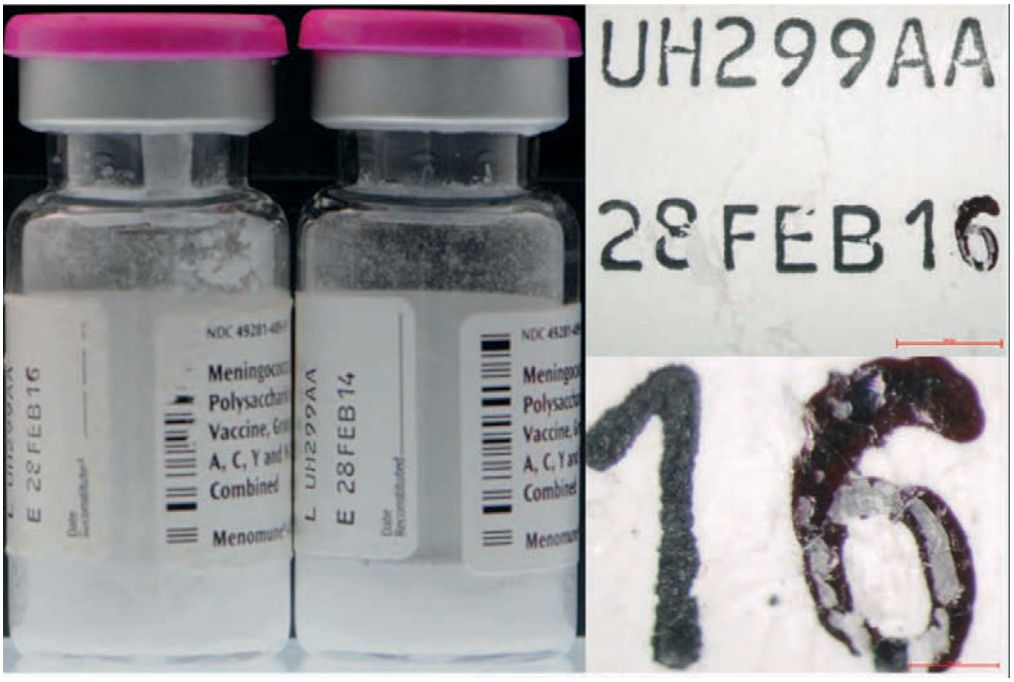


FIG. 12: FALSIFIED MENINGITIS VACCINE REPORTED FROM NIGER IN 2017, IN PROFESSIONALLY PRINTED PACKAGING

Policies can sometimes exacerbate restrictions on supply

Sometimes, access to safe and cost-effective medical products is restricted owing to cultural reasons or patient preferences.

One such product is misoprostol, a medicine used to treat stomach ulcers. The active ingredient can also be used to induce labour, although WHO warns against its use in early pregnancy because of the risk of haemorrhage. It seems, though, that many women unable to access contraception to prevent an unwanted pregnancy use misoprostol to try and terminate it early, at some danger to themselves. Several websites explain how to use the product as a vaginal suppository, a clear indication that it is being offered in some countries for uses for which it is not licensed.

In recent years, police in various Latin American countries have discovered unregistered laboratories

making falsified medicines, which they believe are part of a network. Many of these are manufacturing falsified contraception, as well as misoprostol. In Asunción, the capital of Paraguay, for example, at least three laboratories were dismantled within a period of just a few months in late 2013 and early 2014; in July 2017, a televised report by police in a different area of Paraguay stated that raids on another underground laboratory had again found large quantities of falsified misoprostol.

Eleven countries on three continents have already reported suspect substandard or falsified contraceptives to the WHO database, and eight have reported potential abortifacients, including misoprostol. This number is likely to increase while demand continues.

4.1.3 Acceptability

It is a challenge for planners to ensure that they have enough medical products available to meet sometimes unpredictable need. But demand is not just about need. It is also influenced by consumer and service provider preferences, which in turn are affected by marketing practices and incentive structures. Responding to the demand for one formulation, dosing regimen or brand over another is a very difficult task for policy-makers juggling limited resources. Sometimes, the perceived acceptability of a particular product is deliberately manipulated (often by those hoping to make a quick profit by selling a more expensive product). In these cases, the task of the planner hoping to predict demand becomes almost impossible.

Criminals use branding in much the same way as legitimate businesses do: they seek to increase the acceptability of a product by creating an aura of quality around it. The aura of quality created by the packaging used by criminals is an illusion – the contents are anything but reliable.

Unethical practices can influence demand

In countries at all income levels, health workers are often relatively poorly paid, especially if they work in the public sector. In some countries, formal pay scales are well below subsistence levels, and health workers may have to supplement their income through formal and informal mechanisms. These include encouraging patients to choose more expensive medicines, the producers of which may pay a commission to the health worker, rather than generic medicines provided by the health system either free of charge or at a lower cost (*31*). Marketing practices in wealthy countries can also encourage the prescription of more expensive medicines that consumers who are not fully insured can ill-afford (*32*).

A recent case in Indonesia demonstrates how this systemic weakness can threaten patients. Indonesia has a relatively strong national immunization programme – vaccinations using locally-made generic vaccines certified by WHO's prequalification programme are provided free to children nationwide. There is no question of stockouts, nor of vaccines being unaffordable. But health workers sometimes actively promote the use of imported equivalents, telling parents that these are of higher quality, and have fewer side-effects. Although only about 1% of vaccines in Indonesia are imported, many of Indonesia's middle-class parents are happy to pay for these products. That generates income for health centres and their staff, but it also puts upward pressure on the limited supply of imported vaccines. The more cheaply health centres can source the imported vaccines, the more money they can make from selling them.

This proved a temptation to a sizeable network of criminals and their accomplices in health centres. According to Indonesian police, used vaccine vials were collected up from health centres, and refilled in a number of warehouses that had been made into unlicensed vaccine factories. These factories were making useless products purporting to protect against a dizzying array of diseases, including diphtheria, pertussis, tetanus, polio, meningitis and pneumonia. The vials were filled with a mixture of cheap vaccines, saline solution, and in some cases antibiotics, relabelled and repackaged as though they were expensive imported brands. They were then sold back to health centres at a considerable discount compared with the genuine product. Indonesian regulators found the falsified vaccines in 37 hospitals and health centres in 2016, and police said their investigations suggested the network of criminals had operated for more than a decade, and had been active nationwide. Several of the suspects had trained as pharmacists, but none was licensed to produce or sell vaccines. Two doctors and a midwife were among those arrested (*33,34*).

The Indonesian Ministry of Health believes that around 5000 children received the falsified vaccines in 2016 alone. There were no reports of harm to individual children, although they were obviously left unprotected against the diseases for which they had supposedly been vaccinated. However, widespread press coverage shows how badly the incident damaged people's confidence in both vaccination and in health care workers. Vaccination programmes are one of the most cost-effective interventions against infectious diseases, and they are especially important in countries such as Indonesia which have recently made massive strides towards achieving universal health coverage. Relatively new pooled insurance systems may be overwhelmed if vaccine-preventable infectious diseases spread, requiring expensive treatment.

Low price is not protection against falsification

While press coverage often focuses on the falsification of high-priced medicines, the cases reported to the WHO substandard and falsified medical products surveillance database make it abundantly clear that those involved in the production and supply of falsified medical products are attracted by profit margins, rather than just price differentials. Even low-priced medicines can make money for criminals, as long as the sales volume is high enough. As Table 1 in section 3.3 showed, antibiotics (many of which sell relatively cheaply, but in huge quantities) account for 17% of the falsified products reported so far. The trick for criminals is to make their low-priced falsified products acceptable to large numbers of consumers. They do this by hijacking marks of quality.

Global health financing mechanisms such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Gavi the Vaccine Alliance, have established bulk purchasing and distribution systems that aim to keep prices down and secure stocks of key medical products for hundreds of millions of people in lower income countries. The Global Fund, for example, had financed more than 626 million malaria treatments by mid-2016. Many of these were acquired through a pooled procurement mechanism that buys generic and other low-cost medicines. Quality-assured medicines are provided at subsidized prices through the private sector, which is where more than half of the patients in sub-Saharan Africa get their malaria medicines (*35*). Although the subsidized medicines come from a variety of manufacturers, most are branded with the Green Leaf logo, intended as a collective mark of quality. In 2012, a survey of outlets selling antimalarials in seven African countries found that most retailers in the majority of the countries recognized the logo. When asked what it meant, most of the retailers in five of the countries responded "effective/quality anti-malarial" (*36*).

Although Green Leaf medicines are sold at prices that are low relative to other, equivalent products in the private sector, the sales volume is huge. This has proven attractive to people with the capacity to falsify medicines on an industrial scale. In 2012, customs officials in Angola were inspecting a shipment of goods from southern China that included children's bicycles, bras, hair extensions and loudspeakers. Inside the loudspeakers, the customs officials found pornographic videos, and Coartem, a malaria treatment. Thirty-three million doses of Coartem were discovered – enough to treat more than half of Angola's annual malaria cases. The tablets were packaged in boxes that carried the Green Leaf mark of quality, as well as the stamp of approval from the Nigerian medicines regulatory agency, suggesting the product may have been intended for markets further afield. Laboratory testing confirmed that the tablets contained none of the expected active ingredients – they would have been useless to a patient with malaria.

Although the seizure was huge, it clearly did not take all the falsified medicines out of circulation. Less than a year later, a very similar product was found in Cameroon, some 2000 kilometres to the north. Indeed, falsified artemether-lumefantrine – sold as Coartem as well as under other brand names – has been reported from 18 countries, as shown in Fig. 13.

FIG. 13: AFRICAN COUNTRIES REPORTING FALSIFIED ANTIMALARIAL ARTEMETHER-LUMEFANTRINE TO THE WHO GSMS (2013–2017)

The Coartem case, along with many others in the database, shows that hijacking names, logos and other packaging elements from established medical products is a preferred method in pharmaceutical crime. Some networks go further, inventing their own "trusted brands" through the use of other logos, including that of WHO, as described in section 5.2.2.

4.2 Lack of good governance

As Fig. 7 showed, and as many of the examples above confirm, falsified and substandard medical products often reach patients because of a failure of governance. In this context, governance is a very broad term: it covers the rules that control the manufacture and trade of medical products and the systems that monitor them. Governance also refers to the laws that underpin existing rules and regulations, and the institutions that enforce those laws. The term includes poor ethical practice through to corruption in both the public and private sectors.

4.2.1 Overstretched regulatory frameworks

Sometimes, governance fails because there are not enough well-trained people, functioning laboratories or temperature-controlled warehouses to ensure that the rules are followed adequately: those cases are discussed in section 4.3 on technical capacity. Other cases, some of which have already been described, are more egregious: greed leads to deliberately unethical and criminal behaviour, and current governance structures are often not strong enough to hold perpetrators to account.

The need for a strong regulatory network

The pharmaceutical trade has become a web of international exchange. As middle-income countries improve their technical capacities and industrial bases and more countries start participating in pharmaceutical production, the multinational provenance and global journey of a single bottle of

tablets is likely to grow even more complex. This global interconnectedness must be mirrored by regulatory structures that allow national authorities to exchange information and skills quickly and efficiently. The WHO GSMS aims to provide regulators with just such an information hub.

Regulatory structures must adapt to existing realities. Currently, a very high proportion of affordable generic medicines are made in just a handful of countries. Yet the national regulatory authorities in those few countries have only limited responsibility for assuring the quality of products sold outside their home markets – that duty falls to dozens of importing countries, each with a regulatory structure that duplicates the functions of its neighbour. This "buyer beware" axiom makes sense in principle – governments are, after all, ultimately responsible for protecting the health and welfare of their citizens and thus, by extension, for assuring the quality of medicines nationally. But because of the capacity limitations discussed in section 4.3, as well as the globalization of the pharmaceutical industry, it is less sensible in practice.

No country has the capacity to inspect tens of thousands of different medical product formulations coming from hundreds of different manufacturers. Often, the best they can do is to assume that if the product is manufactured in a well-regulated country, it will be of acceptable quality. That is generally a safe assumption, especially where cooperative agreements allow the importing regulator to carry out due diligence checks with regulators in producer countries. However, even in some of the most regulated markets such as the European Union (where the work of the pan-European regulator is reinforced by agencies in each nation state), falsified medicines sometimes slip through the net. As in any market, they are especially likely to escape detection if the falsified product is sold exclusively to less regulated markets.

In 2013, a pharmacist working in west Africa discovered a supermarket bag full of partially packaged malaria medicines, being dispensed free of charge in a public health centre (Fig. 14). The name of a French group of companies was shown on the blister packs.

The matter was reported to the WHO GSMS, who passed the information on to the French regulatory authorities. Their investigation confirmed that the company was only licensed to manufacture herbal products. A raid of the factory by French law enforcement agents working with national regulators revealed that the medicines were not produced in accordance with required standards. Analysis of samples showed that the antimalarial medicines were subpotent and would not effectively treat patients. More than 8 million doses of these poor-quality malaria medicines had been distributed in sub-Saharan Africa over the course of 2012.

During the inspection, it was revealed that the same group of companies also manufactured and distributed a rapid diagnostic test for malaria – for which there was no marketing, nor manufacturing authorization. More than 6000 of these unauthorized rapid diagnostic tests for malaria had been sold between 2013 and 2014.

The Paris High Court imposed a total of €110 000 in fines on the various companies and people involved in the manufacture and distribution of these unauthorized and poor quality antimalarial products. Two pharmacists were also given suspended prison sentences of 12 and 5 months, respectively (*37*).

It is noteworthy that the judge declared that the subpotent antimalarials posed a threat to human health owing to the risk of the development of antimicrobial resistance linked to subpotent medicines.

FIG. 14: SUBSTANDARD ANTIMALARIAL MEDICINES DISTRIBUTED IN PUBLIC HEALTH CENTRES IN A CENTRAL AFRICAN COUNTRY

The WHO database contains only a few examples of the deliberate production of substandard medical products by licensed manufacturers. Unfortunately, this is unlikely to be because this type of falsification is rare, but rather because it is vastly underreported and very difficult to prove. Active ingredients are almost always the most expensive component of a medicine – for many generic products they account for more than four fifths of production costs – so reducing them is an attractive prospect for unethical manufacturers. The temptation is all the greater because it is exceptionally hard to prove that the deficit is deliberate. That is because there are other possible reasons for a deficit – there may have been a genuine manufacturing error in a single batch, or the product may have degraded since it was made because of poor handling in transit. In addition, medicines that contain half or two thirds of the active ingredient are much less likely to come to regulators' attention than tablets or injectables that have no active ingredient at all, because they will probably have some of the expected effect on the patient, even if it is less than expected. Health care workers sometimes simply raise the dose (potentially increasing shortages), or switch the patient to another medicine. They rarely report lack of efficacy unless it is prolonged or is seen in many patients.

The difficulty in spotting and prosecuting perpetrators of this type of falsification is especially worrying from a public health point of view because, as described in section 2.2, anti-infectives that do not contain or release enough active ingredient to cure an infection are likely to promote drug resistance.

For now, increased support and resources for quality inspection, and regulation of overseas sales in major exporting countries, may compensate for regulatory weakness in importing countries. That regulatory weakness must also be tackled, including by building stronger regional and local ties that streamline trade and lighten the regulatory load by reducing duplication of effort.

Complex crimes require collaborative investigation

The cases of falsification reported to WHO represent a small fraction of the true total. The very fact that they have been discovered and reported internationally means they are also among those most likely to be followed up. The investigation and prosecution of those involved is the responsibility of the competent authorities in the countries in which they are being manufactured, distributed and supplied. Yet, even among the cases in the WHO database, only a minority have led to successful prosecutions.

This is in part because successful prosecution of pharmaceutical crime is very difficult. Most often, falsified medicines only come to light when they reach the retailer or the patient – it is very hard to trace them back through complex supply chains, or to prove where the criminal activity occurred. Successful investigation requires an extraordinary level of collaboration, which is sometimes hampered by governance structures. In some countries, medicine regulators are a unit of the ministry of health; in others they are separate entities. In either case, coordination between the agency or unit charged with oversight of the quality of medical products on the one hand, and the group reviewing pharmacovigilance data and treatment guidelines on the other, is not always smooth. This is usually the result of the siloed structures common to most large institutions; it is sometimes aggravated when the decisions made by these different units affect budgets, for example because they have implications for procurement or generate licensing fees. Whatever the reason, siloed structures mean important information is not always quickly shared.

Meanwhile, in most countries, investigation of criminal activity is the work of the police, who may not have extensive expertise in the specialized techniques sometimes needed to investigate pharmaceutical crime. The situation is greatly complicated because the international nature of much of the trade in substandard and falsified medical products often requires cross-border investigation. Such investigations require a shared legal understanding, often involving mutual cooperation treaties that do not cover all countries. In many regions, there is limited capacity to tackle offshore companies that have complex ownership structures and use foreign bank accounts. Not only will investigations rely heavily on laboratory analysis of the falsified or substandard product, but there will be a need to follow the paper trail of the product to trace its point of origin. The paper trail is now usually an electronic trail. Location of the evidence necessitates forensic examination of computers and smartphones. That requires access to laboratories capable of retrieving that evidence, a complex and expensive process, often unavailable to the countries worst affected by this issue. Language can be an important barrier to effective cooperation, and in areas of regional conflict or political rivalry, international coordination becomes even more fraught, even though these are often the very areas that provide significant opportunities for criminals.

4.2.2 Transparency and accountability

The long journey between tablet formulation and administration to the patient involves many entities: producers of raw ingredients, manufacturers of finished products, transport companies, stock managers, brokers, distributors, and retailers or health facilities, at a minimum. Accountability is thus very hard to establish: it is not always clear where one actor's responsibility ends and another's begins. And yet transparent accountability mechanisms are critical to effective oversight of the production and supply of medical products.

Buyer beware: due diligence is always the first step

As discussed already, the buyer beware principle, exercised at the national level, strains the capacity of regulators. But the same principle applies to people sourcing medicines at every stage of the supply chain. The first level of protection against substandard and falsified medical products for anyone procuring them is simply to check the credentials of the source. This means verifying names and addresses, checking that people really do represent legitimate entities, ensuring that manufacturers, traders or retailers are properly licensed, and if possible, that the products are appropriately registered. During the training for designated national focal points, WHO staff also provide methods for systematic visual inspection. These basic steps are important for products that are new or unusual in a market, because there will be fewer well-established procurement channels.

Yellow fever vaccines provide an example. The disease is endemic in Africa and South America, but not in south Asia. In Bangladesh, the greatest demand for yellow fever vaccine comes from the army, which periodically deploys troops to peacekeeping missions in endemic countries. While the army is adept at procurement, it does not specialize in importing medical products. In the past, it used a medical wholesaler to procure yellow fever vaccine from the Institut Pasteur, which makes the product in Senegal. Then, while preparing its 2016 deployment, the army was approached by a supplier purporting to work

directly with the Institut Pasteur. They bought from him instead. The previous wholesaler was surprised to notice that while the newly procured vaccines had the same batch number as those he had earlier supplied to the army, the expiry date was different. He alerted the Institut Pasteur, which said they did not know the man posing as their agent. The institute confirmed that the vaccine, which bore the wrong combination of batch number and expiry date, was falsified. The authorities in Bangladesh verified that the supplier's company did not exist at the registered address, and quickly ensured that none of the vaccine was further distributed or used (*38*). Laboratory analysis subsequently showed that the product was contaminated with bacteria.

Licensing is an important part of the governance of medical products, but it is only valuable in combination with due diligence on the part of procurers.

At least one instance where due diligence on the part of a manufacturer might have prevented falsification has been reported to WHO – an example of seller beware. The unusual case involved several dozen containers full of common antibiotics, packaged as the product of a European manufacturer and delivered to a country in conflict where normal governance systems were much disrupted. One of the officials in the region, surprised at so large a shipment of medication of an unrecognized European brand, asked for WHO's help with verification.

Although the supposed European manufacturer does not exist, laboratory tests of a small selection of samples showed that most of the medicines tested were, in fact, of acceptable quality. Further investigation led to a manufacturing plant in India, which had produced the medicines on contract for a dealer who had also supplied the artwork for the packaging. Contract manufacturing in lower-cost countries is increasingly common, and poses little problem as long as it happens on behalf of a licensed company in accordance with good manufacturing practices. In this case, however, fake packaging – apparently designed to extract higher prices because of the association with a manufacturer in a high-income country – obstructed verification and batch tracing. While there is no legal obligation on contract manufacturers to verify the credentials of their clients, it might in this case have prevented a sizeable incident of falsification.

Reporting culture is not well established

Front-line health workers, who handle medical products daily and observe their effects, are often first to become suspicious about the quality of vaccines or medicines. Yet they are often reluctant to report their suspicions to the national regulator for fear of reprisals from the criminal networks that produce and distribute falsified medical products, or from health service managers who may have procured the product in ways that were not fully transparent. Legitimate manufacturers and traders who provide information to investigators have sometimes been told by powerful forces in the market that their businesses will suffer if they do not stop cooperating with the investigators. Where there are no transparent accountability mechanisms that encourage reporting and protect those who voice their suspicions, distributors can continue to trade substandard and falsified medical products with impunity at the lower levels of the supply chain. They know they are unlikely to be reported.

Weak responses to falsification

If a falsified product is made or sold by a company licensed to handle medicines, vaccines or diagnostic kits, the company can be sanctioned by regulatory authorities. However, in many cases, sanctions are imposed by the courts. While most judiciaries are now very familiar with cases involving illicit drugs, they do not always understand the potential gravity of pharmaceutical crime. While illicit drugs can certainly be harmful, they are at least taken knowingly. Those who consume falsified medicines are often as gravely threatened, but their exposure to risk is entirely involuntary. Since falsified medicines also threaten family and national budgets and confidence in health services, as well as cultivating drug-resistant infections, one might expect penalties for the falsification of medical products to exceed those for the traffic in illicit drugs. And yet, in most countries, sentences for falsification of medical products are much less severe. In the French case described earlier, those involved received suspended jail sentences, and the largest personal fine was of €10 000 whereas drug smugglers can be imprisoned for lengthy terms and the proceeds of their crimes confiscated (*39*).

The international policing agency INTERPOL believes that organized criminal networks that were once known for dominating the illicit drug market are now targeting the medicine trade because profits are high, the risks of detection and successful prosecution are low, and the penalties, if prosecution does succeed, are almost negligible compared with those incurred for large-scale drug trafficking. While the risk–benefit balance is tilted firmly in the favour of those falsifying the products, the activity is likely to continue.

Laboratory analysis of some of the medicines reported through WHO's medicine quality surveillance system would seem to support this thesis. Falsified malaria medicines have been found to contain sildenafil (commonly known by the brand name Viagra), suggesting that falsifiers switch between pharmaceutical products according to market conditions. Laboratory analysis of malaria medicines has also identified precursor chemicals for controlled drugs such as MDMA (3,4-methylenedioxymethamphetamine, better known as ecstasy), suggesting that the same clandestine laboratory is producing illicit drugs on some shifts, and falsified medicines on others (*40,41*).

Some countries (for example Italy) have proactively trained prosecutors, police and the judiciary about both the dangers posed by falsification and the methods favoured by pharmaceutical criminals. The Council of Europe has also drafted a convention known as the MEDICRIME Convention, which provides countries with a model legal framework for dealing with falsified medicines and other types of pharmaceutical crime that threaten public health. The aim is, in part, to provide a framework that will allow for more international coordination in the investigation of suspect falsified medicines, and in the prosecution of criminals (*42*).

4.3 Weak technical capacity and tools

The cases discussed so far illustrate the role that imbalances in supply and demand and shortcomings of governance play in undermining the quality of medical products all over the world. They show that falsified medicines are produced largely out of greed, while poor governance, coupled with limited capacity for oversight, allows them to reach consumers.

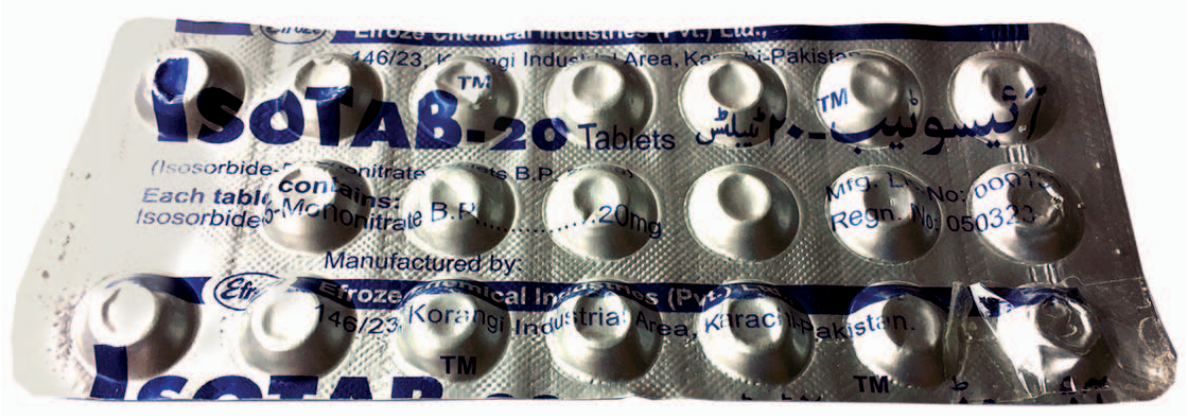
Substandard medical products, on the other hand, are usually the result of a technical deficit coupled with poor oversight. Both are often the result of limited capacity. Good manufacturing practices – well-equipped laboratories; field detection technologies; transport and storage systems that keep products at the right temperature while accurately tracking their whereabouts; competent oversight of production and supply chains – all depend on having the right equipment and well-trained staff. In many countries, some or all of those things are already in short supply, and the rapid expansion of both globalized supply chains and demand in lower income settings is stretching capacity still further.

4.3.1 Following standard procedures: the first step to quality products

Good manufacturing practice (GMP) depends on having standard operating procedures, clearly laid out and easily available, together with trained staff who follow them diligently.

In late 2011, hundreds of patients began arriving at hospitals in Lahore, Pakistan. They were suffering from a darkening of the skin, bleeding and nausea. At first an outbreak of dengue fever was suspected but was later ruled out. Experts were baffled: however, suspicion began to focus on a suspected adverse drug reaction. All of the hospitalized patients had attended the same cardiac hospital and were taking a range of medicines. Dispensing of those medicines was suspended and samples sent to a number of laboratories. Analysis showed one of the cardiac medicines was contaminated with lethal levels of an antimalarial (Fig. 15). More than 200 patients died and 1000 were hospitalized during this crisis. Once the cause of the contamination was identified, treatment was quickly administered. The Government of Punjab established a judicial enquiry tribunal which determined that the contamination was a result of poor manufacturing standards that had led to an active pharmaceutical ingredient being confused with an inert excipient (*43*).

FIG. 15: CONTAMINATED MEDICINE THAT CAUSED HUNDREDS OF DEATHS IN PAKISTAN IN 2011–2012



Another example comes from the Democratic Republic of the Congo, where, in 2014, reports started arriving from health facilities that patients were complaining of being listless and feeling sick. Health staff found they had low blood pressure; in pregnant women this slowed the fetus's heartbeat, potentially damaging its growth. Investigators from the national pharmacovigilance programme carried out a rapid and thorough investigation, and discovered that everyone affected had taken the same locally manufactured paracetamol for headaches and pain management. Regulators quickly suspended production and quarantined all remaining stock of the product.

Preliminary testing locally found that the paracetamol tablets did indeed contain the expected active ingredient. However, analysts with limited exposure to the complexities of the trade in substandard and falsified medical products do not always know what other contaminants or production errors they might look for. With support from WHO, the paracetamol tablets were further analysed in a European laboratory. They were found to contain different ingredients, sometimes at wildly different doses. All the tablets contained some paracetamol – some as much as 500 mg, some just a fifth of that. But many also contained the barbiturate phenobarbital, which slows down breathing and the heart rate, and is a common treatment for epilepsy. Bafflingly, these very inconsistent formulations all carried the same batch number – a clear sign that standard manufacturing procedures were not followed.

This case highlights the challenge of developing local production of medical products in settings where infrastructure and technical capacity are still limited, and where the institutions that support and oversee production quality may be underfunded or understaffed. Many lower income countries are working on expanding their domestic production of pharmaceuticals, in part, perhaps, as a way of reducing the need to import products that are either expensive or of dubious provenance. If quality is to be assured consistently, the industrial expansion must go hand in hand with investments in the systems needed to ensure that correct production and distribution standards are maintained.

Good distribution practice: neglected but essential

Medicines that met the correct specifications when they left the factory can be substandard by the time they reach patients, because they may have degraded during transport or storage. Medicines can lose their potency because they were not packaged properly, because they were not protected from the elements during transport, or – commonly – because they are transported or stored at temperatures or levels of humidity at which their active ingredients become unstable.

In an ideal world, standard operating procedures would regulate all steps of distribution and storage in the same way that they regulate manufacturing. In practice, however, this is often not the case. In most countries, the government's central medical stores are among the best regulated pharmaceutical storage spaces nationally, with reliable temperature control and appropriate inventory systems. But before they get there, medicines have often travelled long

distances in freight containers that are not adequately temperature-controlled, and they may also have been held at docks in high temperatures for several weeks awaiting customs clearance. After they leave well-managed warehouses, medical products are sent to hospitals and dispensaries that may have erratic electricity supplies and limited cold storage facilities. Sometimes, they are displayed on market stalls, again in uncontrolled conditions. The photograph below illustrates disorganized and poor storage conditions at an illegal medicines outlet in west Africa (Fig. 16).

FIG. 16: BEHIND THE COUNTER OF AN UNREGULATED MEDICINES OUTLET IN AFRICA

It is particularly hard to ensure good distribution practices for medical products because of the weak regulatory structures. While national regulatory authorities are tasked with overseeing storage and distribution of products destined for their own citizens through the public sector, they often have less influence over the private sector, or over products supplied by international donors. And, perhaps more importantly, often there are no clear oversight structures for medicines in transit. That means that there is minimal regulatory oversight of conditions either during shipment or in the many transit points through which a single medicine might pass on its journey from maker to market.

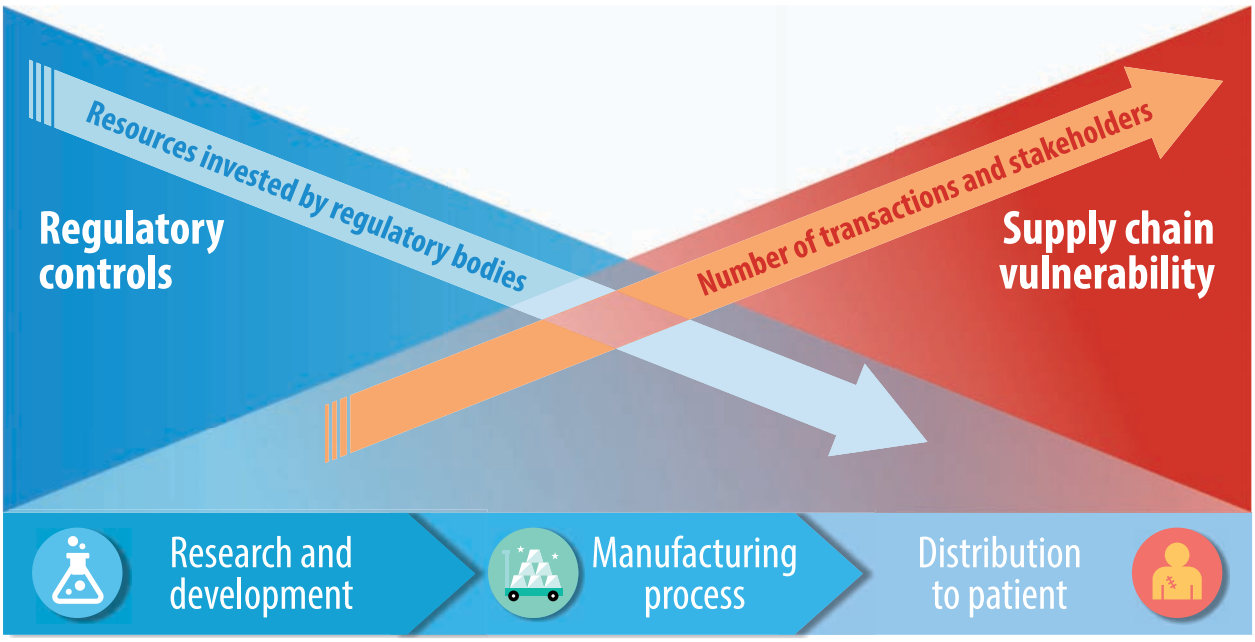
For falsified products, there is no question of oversight of the conditions of transport, since the products should not be in the supply chain in the first place. But that is very difficult to ensure, for the obvious reason that the sellers (and sometimes also the buyers) of these products often go to great lengths to keep them off the regulator's radar. In July 2013, for example, the Nigerian Agency for Food and Drug Administration and Control seized 150 000 doses of an emergency contraceptive. They did exceptionally well to find it: the falsifiers had split the consignment, sending blister packs of tablets in one box and flat-packed the cartons in which the blisters were to be packaged in another box. Both were labelled as containing mobile

phone covers, and indeed they did – the falsified tablets and packaging were buried underneath that legitimate consignment (Fig. 17). The products, which imitated a WHO-prequalified version of an essential medicine, contained no active ingredient. While in this case they were seized at the port of entry to Nigeria, many falsified products find their way into the supply chain, eventually reaching patients.

FIG. 17: FALSIFIED EMERGENCY CONTRACEPTIVES CONCEALED IN MOBILE PHONE COVERS

As distribution spreads geographically and outlets multiply, oversight capacity becomes stretched. As Fig. 18 shows, it tends to be weakest closest to the patient. And of course for products distributed over the Internet, effective oversight of the supply chain is virtually impossible. As the medical product moves through its life cycle towards the patient, it is less frequently subject to regulatory controls, whilst the number of stakeholders and transactions increases. This raises the risk that substandard and falsified medical products enter the supply chain on the final part of their journey to the patient.

FIG. 18: STRENGTH OF REGULATORY OVERSIGHT AT DIFFERENT STAGES OF THE SUPPLY CHAIN



Basic infrastructure, and the skills to use it, are vital to maintain medicine quality

Standard operating procedures and protocols are of little use without the tools, personnel and associated budgets needed to operationalize them. Those tools are very often in short supply, especially in the areas where the other factors that facilitate trade in substandard and falsified medical products are most commonly found. And the tools that do exist are not always in the hands of the people who need them most.

Drug quality testing technologies are a case in point. In several of the cases cited so far, including that of cough syrup in Pakistan and Paraguay, ephedrine in Afghanistan and paracetamol in the Democratic Republic of the Congo, national authorities could not perform the sophisticated tests that would allow them to ascertain the composition of a medicine that was apparently harming patients. Some of those who might have had the technical capacity to do laboratory analyses could not obtain the expensive or restricted reference standards against which to test the medicines. And while front-line customs staff are most likely to encounter potentially low-quality medicines before they enter the national supply chain, and front-line health care workers are most likely to spot them once they do, it is very rare indeed for either of these groups to have access to simple field tests that would help them to triage suspect products. Where field testing equipment is available, staff do not always have the training or the time to use it correctly or consistently.

Sometimes, a lack of simple equipment such as incinerators prevents hospitals and health centres from following correct protocols for disposing of expired products, empty vials and other packaging (Fig. 19). A recent study in Uganda, for example, pinpointed limited access to incinerators, and high fees for their use, as a factor contributing to expired medical products being held for a mean of six years in public facilities (*44*). And as the Indonesian vaccine case described on page 28 so clearly shows, criminals are only too happy to seize on any opportunity to acquire discarded packaging, recycling it to disguise lucrative falsified vaccines or medicines.

FIG. 19: EXPIRED MENINGITIS VACCINES AWAITING DESTRUCTION IN A PRIVATE PHARMACY

Even with the best equipment, regulators cannot function properly if there are simply not enough appropriately trained people to do the job. In an assessment of regulatory capacity in 26 countries in Africa published in 2010 (*45*), WHO concluded: "On the whole, countries did not have the capacity to control the quality, safety and efficacy of the medicines circulating on their markets or passing through their territories."

A CASE IN POINT

One serious case reported to the WHO substandard and falsified medical products surveillance database by an NGO, concerning the Democratic Republic of the Congo, brings together many of the elements known to increase the risk that patients will be harmed by substandard or falsified medicines, illustrating how they reinforce one another.

The case took place in late December 2014 in the Ituri district, which borders Uganda and South Sudan. It came to light when dozens of people, 60% of them children, began to shiver, then to have fits involving stiffening of the neck and other distressing symptoms collectively known as dystonia. Families reported to health workers that they were being shunned by their neighbours, who feared the affected households had been cursed.

Local health staff did not recognize the symptoms, and the Ministry of Health consulted doctors from the NGO Médecins Sans Frontiers who were present in the country. They were equally unable to pinpoint the cause. Authorities first suspected meningitis, but 95% of patients tested were not infected with the bacteria that cause that disease. Other suspected causes were a new unknown disease, or environmental poisoning. Soil and water samples were tested but yielded no clues. The caseload continued to increase (Fig. 20).

A wide range of toxicologists were asked to review videos of the affected children. They suggested another hypothesis: that the dystonia might be caused by toxic drugs. Health staff collected urine from affected patients, and also collected 39 medicine samples from pharmacies and health centres. Because there was no well-equipped laboratory available locally, the testing was performed in France, slowing down access to the results. All nine urine samples tested positive for haloperidol, an antipsychotic medicine used to treat schizophrenia. Overdoses of haloperidol are known to cause muscle spasms and rigidity, and can sometimes leave patients in a coma. Laboratory technicians then started to look for haloperidol in the medicines: they found it in nine tablets (six of them collected from patients, three from sales outlets). On average, those tablets contained 13 mg of the drug, about 20 times the maximum recommended dose for a child. And all nine were labelled as something completely different – diazepam, a medicine more commonly known by the brand name Valium, often used to treat anxiety.

By the time the source of the problem was identified, 930 people had been hospitalized with dystonia, and 11 had died.

Some of the haloperidol tablets were packaged in bottles stamped in red with the words: "Government of Uganda. For public use only, not for sale". Further investigation, supported by WHO, determined that the diazepam bottles were apparently genuine, bearing a correct batch number and expiry date together with the trademark of the product's manufacturer. That manufacturer does not, however, make haloperidol. Other bottles labelled as diazepam were also apparently completely falsified. Haloperidol had found its way to the Democratic Republic of the Congo repackaged as diazepam. Local oversight mechanisms were not strong enough to reinforce due diligence procedures. Had the institutions acquiring the medicines checked, they would have found out that at least one of the manufacturers listed on the packaging does not even make diazepam.

The falsifier's marketing strategy raises the question: why was there such a large market for diazepam in Ituri? The district has a long history of conflict and a large population of displaced people who have suffered from a shortage of medicines. Investigators were also told that children were given the medicine because it was believed to reduce shivering and fevers associated with malaria. This is clearly an irrational use of the product; many antimalarials would do the job much better, while also clearing the infection. However those medicines are not always available in this remote and conflict-ridden part of the country, so people use whatever they can get. In this case, shortages of more appropriate products may have been exacerbated by changes in central government policies. Just before the outbreak of dystonia, subsidies that underwrote the

distribution of medical products from central stores to the periphery had been temporarily cut.

When the falsification was confirmed, WHO issued an international medical product alert, notifying neighbouring countries of the need to be especially vigilant about diazepam. The national regulatory authority issued a recall for all diazepam in the affected region, and temporarily banned further distribution. While this was an understandable response, it may not have had the desired effect. If the recall and distribution bans were effective, they would have increased shortages of a product known to be in high demand in an area with a very porous border. That may in turn have increased the temptation to fill the gap with more falsified medicines.

Many factors driving the production and distribution of falsified medicines are illustrated by this case. Poor infrastructure and conflict limit access to quality medicines; policy changes at the central level have perverse effects locally; irrational use of medicines creates a market which can be filled with substandard or falsified products; weak regulatory capacity reduces motivation to conduct due diligence; poor international collaboration mechanisms lead to missed opportunities for detection; lack of field detection technologies and laboratory capacity impede detection and increase time to effective response; and a disproportionate response potentially increases shortages.

The case also demonstrates what can be achieved when many actors work together. An NGO, national health service providers, national regulators, an international team of toxicologists, laboratories and WHO all worked together to discover the cause of the unexpected outbreak of fits and seizures and alert others to the threat. Once they had pinpointed haloperidol masquerading as diazepam as the cause, they could propose an antidote. An ironic coda to this episode: the antidote to an overdose of haloperidol is (good quality) diazepam *(46)*.

FIG. 20: THE MEDICAL CENTRE SET UP BY MÉDECINS SANS FRONTIÈRES WHERE PATIENTS AFFECTED BY THE FALSIFIED DIAZEPAM WERE TREATED

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5. SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS: THE SOLUTION

As discussed above, trade in medical products that are falsified, poorly made or degraded threatens health in every region. Driven by globalization of trade and the increasing complexity of supply chains, it is likely to increase unless serious, well-resourced efforts are made to tackle the issue.

This chapter summarizes what needs to be done to:

- **PREVENT** the manufacture, sale and consumption of substandard and falsified medical products;
- implement systems to **DETECT** any substandard or falsified products that are already in the supply chain;
- **RESPOND** quickly and proportionately to any incidents that are detected, in ways that safeguard patients and the supply chain, take appropriate action against those responsible, whilst not causing unnecessary shortages.

Most of these actions require the coordinated participation of a number of different actors, including national and regional governments; global organizations; the private and non-profit sectors; and civil society. Effective action also requires close collaboration between disciplines: health authorities must work with customs and law enforcement agencies; pharmacovigilance systems must link to those that track antimicrobial resistance and falsified products; pharmaceutical and logistics companies must exchange information with regulators; patient and consumer groups must interact fluently with authorities. While many of these relationships already exist, all must be strengthened and expanded to maximize the chance of success.

WHO itself contributes to these actions in many different ways. Technical efforts are led by the Safety and Vigilance Unit of WHO's Essential Medicines and Health Products Department, which aims to strengthen national and global responses in the three areas depicted in Fig. 7, improving affordable access to quality, safe and effective medical products; strengthening governance and regulatory capacities; and improving technical capability. However, many other programmes and divisions within WHO are also involved, including disease-specific programmes which are themselves challenged when medicines, vaccines or diagnostic kits do not work the way they should. Regional and country offices also play a role. This chapter begins by providing an overview of two actors that stand at the core of WHO's activity in this area. Their specific contributions to preventing, detecting and/or responding to the threat of substandard and falsified medical products are described in section 5.2 together with the contributions made by other parts of the Organization.

5.1 At the core: guidance and evidence

WHO collaborates with many partners in responding to substandard and falsified medical products. Within the Organization, however, the response is steered by the Member State mechanism on substandard and falsified medical products, supported by evidence provided by the WHO GSMS, among others.

5.1.1 Coordinating progress: the Member State mechanism on substandard and falsified medical products

The response to substandard and falsified medical products is seen as a high priority by Member States. In 2012 the World Health Assembly established a unique structure known as the Member State mechanism specifically to provide oversight, strong commitment and political will from Member States and WHO to tackle this issue. It brings all 194 Member States of WHO together in a voluntary, self-governing body with a steering committee that includes a chair and vice-chairs representing all WHO regions. It is supported by a secretariat made up of WHO staff. It was formed to increase Member State collaboration around

protecting public health by preventing and controlling substandard and falsified medical products. That collaboration was much needed. Early attempts to address the issue on a global scale were hampered by discussions over whether protection of public health should include consideration of intellectual property rights. The Member State mechanism has now firmly resolved that debate, recognizing that the threat to lives and well-being posed by substandard and falsified medical products can be dealt with most effectively by focusing exclusively on issues of public health concern.[5]

A 2017 review of the first five years of the mechanism's work observed that time spent building trust between nations around a common agenda in the early years is now bearing fruit. The body has simplified and clarified definitions of substandard and falsified medical products, and supported the development of the WHO GSMS. The Member State mechanism is contributing to the development of the evidence base in other ways too. For example, it commissions and guides studies that will increase our understanding of the factors that lead to falsification and poor production and distribution practices. A study of the public health and socioeconomic impact of substandard and falsified medical products is published in conjunction with this report.

Working groups led by Member States have also made important contributions in several technical areas, which will help countries to prevent the production and sale of these potentially dangerous products, and detect and respond to them when they do occur. These are discussed in section 5.2 and a summary of the objectives of the technical documents published by the Member State mechanism is provided below.

BOX 5: Objectives of the technical documents published by the Member State mechanism

- Identification of factors that drive the emergence of substandard and falsified medical products
- Recommendations for health authorities to detect and deal with substandard and falsified medical products
- Developing a national action plan to prevent, detect and respond to substandard and falsified medical products
- Creating a global regulatory focal point network
- Implementing track and trace systems
- Understanding authentication technologies
- Reaching a global common understanding on the definitions of substandard, unregistered/unlicensed and falsified medical products

Source: http://www.who.int/medicines/regulation/ssffc/mechanism/

[5] The mechanism was formerly known as the Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products. The new name, adopted by WHO's governing body in May 2017, reflects the mechanism's success in achieving consensus around definitions.

5.1.2 Providing and using the evidence: WHO Global Surveillance and Monitoring System

WHO's GSMS aims to support WHO Member States in minimizing the risks to public health posed by substandard and falsified medical products. To achieve this aim, GSMS staff work to:

- train and support a network of **nationally designated focal points within national and regional regulatory agencies** who act as a channel of communication between national and global authorities around medicine quality;
- develop **tools and systems** that countries can adapt to make reporting of suspected products easier and more efficient;
- support countries in appropriate public-health focused **investigation and response** to incidents involving substandard and falsified medical products;
- develop and maintain a **global database** of reports relating to the discovery of substandard or falsified medicines, for use by regulatory agencies globally;
- analyse global data to provide **evidence-based recommendations** for appropriate decision-making and effective action.

Activities that aim to support specific capacities to prevent, detect or respond to the threat posed by medical products that are falsified, poorly made or degraded are discussed in section 5.2.4. However, some of the structures supported by the system increase capacities across all three areas, and are described in more detail here.

A global network of trained national focal points

At the core of WHO's medicine quality surveillance system stand individuals mandated by national medicine regulators or health ministries to exchange information about medicine quality with colleagues globally. Trained by the Geneva-based Substandard and Falsified Medical Products Group, they are able quickly to alert the global body, as well as a range of partners nationally or regionally, if substandard or falsified medicines are suspected in the national supply chain. Just as importantly, they pass on to their own national authorities relevant information deemed of international importance by other countries reporting to the WHO Substandard and Falsified Medical Products Group. This keeps everyone up to date about the highest risk products in the global supply chain.

The largest number of trained focal points are currently in sub-Saharan Africa, where most training courses have been held. This is in part because regional authorities recognized a high concentration of risk factors for imperfect medical products. The potential public health gains of increased capacity to detect and respond to such products in the region are thus especially high. Although some regions are underrepresented, the Member State mechanism recently requested that every WHO Member State officially designate and support a focal point – an indication that this approach is already proving itself useful.

Training for focal points is increasingly provided in collaboration with other partners who have particular expertise in technical areas such as sampling methods and sample handling. The training focuses on risk awareness, investigation protocols, reporting and coordination mechanisms and risk communication.

A global database of substandard and falsified medical products

The reports that come from countries are compiled into a single, global database by staff in Geneva. This database underpins national efforts to detect and respond rapidly and appropriately to suspect products, as well as providing an evidence base that helps prevent future occurrences of falsification or unacceptable production or distribution practices.

The team in Geneva liaises closely through the national focal point with national regulators, and sometimes manufacturers and other partners too, in order to develop detailed descriptions of each incident. Incidents are also coded to highlight the particular vulnerabilities underlying the case – stockouts due to diversion, for example, or poor manufacturing practice.

This allows analysts to spot patterns over time and space – information that can be used to guide further investigation and response.

The global surveillance system is currently maintained by a small team of professional staff who – besides entering data – discuss cases at length with focal points, arrange and participate in follow-up action if requested, and issue regional and national alerts. Importantly, they also analyse the data on an ongoing basis, ensuring that the data are actively used to inform decision-making in countries and at the level of the Member State mechanism. For example, in March 2014, less than a year after the full launch of the database, system staff produced a report on access to and use of laboratory analysis for products suspected of being substandard or falsified. At the time, 314 suspect products had been reported, the majority of them from sub-Saharan Africa. Analysts found that just over half underwent nothing more than visual inspection. Although lack of laboratory capacity is frequently cited as a reason for incomplete investigation, deeper interrogation of the data found this was only the case for 10% of the untested products. Expense of testing, lack of reference standards for comparison purposes, equipment that was defective, no means of recalibrating equipment, no means of servicing equipment and shortage of qualified staff were all weaknesses identified. Findings such as these can guide rational decisions about where to invest resources in strengthening systems to prevent, detect and respond to the threat of substandard and falsified medical products.

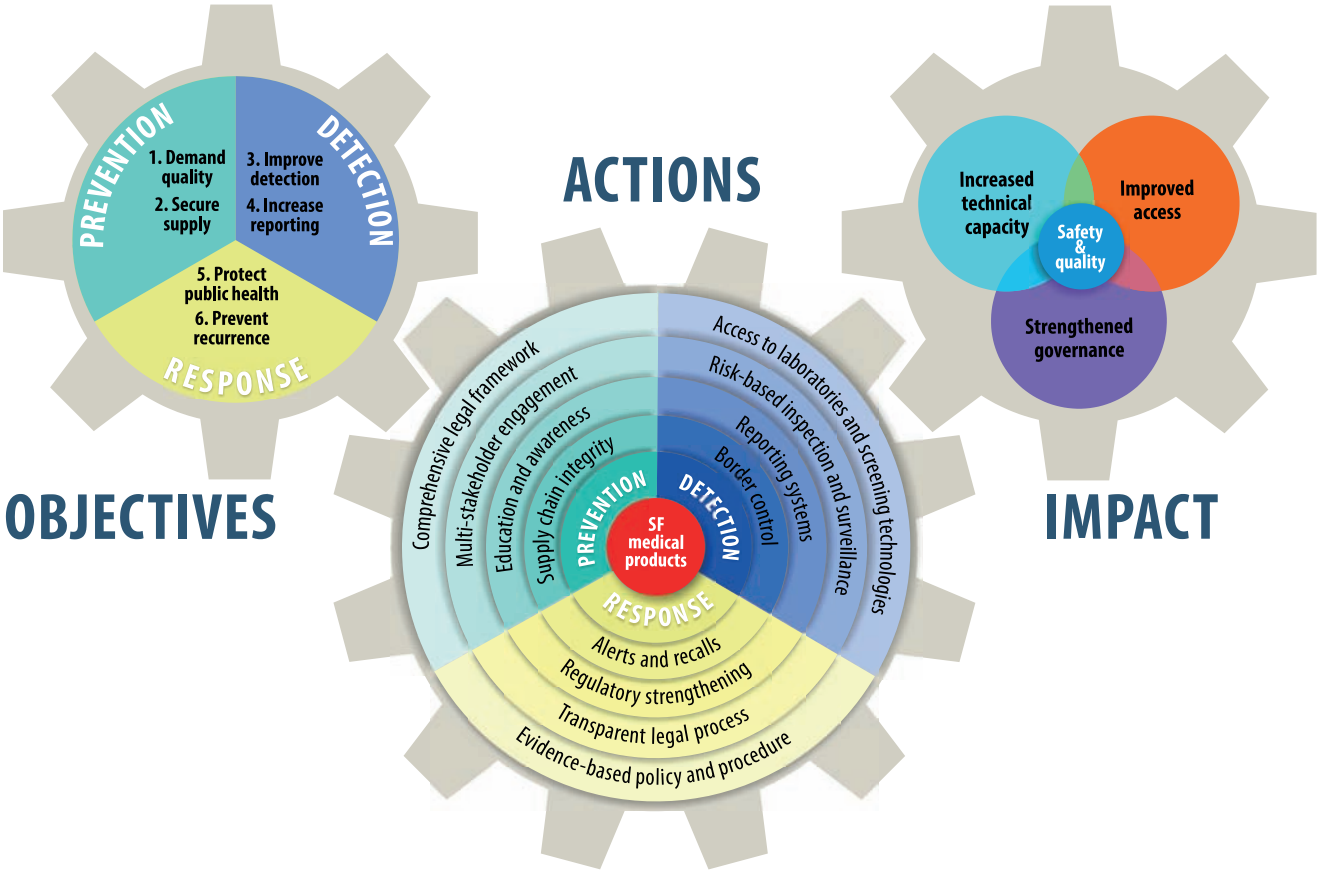
5.2 Prevent, detect, respond: a virtuous circle

"Prevent, detect, respond" sounds deceptively simple. Like the factors that facilitate the production and sale of medical products that fail to meet quality standards, however, the actions and systems needed to achieve these three aims overlap. For example, it means that action taken principally in response to the discovery of a substandard or falsified medical product in one market can help detect it quickly in others, and perhaps prevent its occurrence in the future. That dynamic was seen in the case of cough syrup in Pakistan and Paraguay described at the beginning of this report. Pakistan's response helped with the rapid detection of contaminated product in Paraguay and other countries. Colombia and Peru were able to prevent dangerous cough medicines reaching patients, and Indian authorities were able to ensure that the production errors that led to the contamination were corrected. Similarly, the detection of substandard paracetamol in the Democratic Republic of the Congo triggered factory inspections which led to enforcement of better manufacturing practices, thus improving quality of the product made at that facility and reducing the risk of errors being repeated.

The interaction between various initiatives needed to prevent, detect and respond to substandard and falsified medical products underlines the critical importance of coordination across sectors and disciplines.

Fig. 21 sets out the objectives, actions and the impact of tackling substandard and falsified medical products using the three-pronged strategy of prevention, detection and response. While these three areas interconnect, the components shown are seen as the key elements that need to be in place. Countries can tailor the strategy according to their capacity and capabilities.

FIG. 21: PUTTING PREVENTION, DETECTION AND RESPONSE INTO MOTION



*S&F : substandard and falsified medical products

5.2.1 Prevention

There would be no need for detection and response if the production of substandard and falsified medical products or their access to the supply chain could be prevented in the first place. Humans make mistakes, machines break down, and the promise of making a lot of money through illicit means will always appeal to a small but unscrupulous minority. However, there is much that can be done to reduce the likelihood that errors occur, or that the ill-intentioned pick the falsification of medical products as their crime of choice.

Education and awareness

Education and awareness among all stakeholders is seen as the first step in preventing the use of substandard and falsified medicines. Providing accurate and balanced information on the risks of substandard and falsified medical products, how to avoid them, how to spot them and how to report them is critical to help drive consumers from informal markets to safer outlets.

A raised awareness among those most threatened by substandard and falsified medical products – patients – as well as the health care workers who treat them, can also be invaluable for detection. Many of the incidents in the WHO surveillance database were initially reported to regulators either by patients themselves or by front-line medical staff, including pharmacists.

One especially interesting case of falsified products entering the regulated supply chain was initially detected by a patient who reported his suspicions to the authentic manufacturer, and separately by an importer who reported suspicions concerning the same product. In this case, the patient had been taking his medication for a chronic disorder and had observed an unusual change in the physical appearance of the tablet. This demonstrates how well patients know their medicines and the importance of raising awareness, improving information feedback flows with health care professionals and national regulators, and having effective reporting systems.

A greater investment in public awareness and knowledge about medicine quality could potentially reduce the market for substandard and falsified medicines and diagnostic kits by encouraging people to be more exacting about the products they buy and the sources they buy them from. It might also make patients and health workers more likely to think carefully about their medicines, reporting any that are suspect, thus contributing to more detection.

As the case of falsified vaccines in Niger described on page 26 illustrates, sensitization efforts by trained focal points are already raising awareness among health care workers, reinforcing practices of due diligence, giving them clues as to what to look for, and providing them with clear procedures for reporting any suspicions.

Preventing shortages by assuring access

As discussed in Chapter 4, limited access to affordable, quality medical products creates a vacuum that is frequently filled with alternatives that are falsified or of poor quality.

Although shortages persist, access to many medical products is much easier now than it was just a decade ago, in large part because of the leadership shown by WHO's Essential Medicines Programme, and active partnerships with others in the field of global health including UNICEF, the Joint United Nations Programme on HIV/AIDS (UNAIDS), Gavi, and the Global Fund for AIDS, Tuberculosis and Malaria, to name just a few. Bilateral donors, philanthropic foundations and national governments have also played a vital role in improving access to affordable medical products, as have WHO and partner programmes that are responding to specific infectious or noncommunicable diseases and reproductive health needs. An important part of that contribution has been their support for the development of medicines and diagnostics that meet the needs of resource-constrained settings, and for the use of quality-assured generic medicines.

As the supply of affordable medicines in low- and middle-income countries improves, new access challenges grow in importance. Stubbornly high prices for medical products and consultations in some of the highest income countries present an ongoing challenge. As long as these persist, consumers are likely to turn to the Internet both for information and medical supplies. This growing culture of self-diagnosis, self-prescribing and self-treatment opens the door to relatively easy infiltration of poor products into the supply chain. Irrational use of medicines is another challenge.

Promoting the rational use of medicines

Teams working to combat the spread of drug-resistant infections emphasize the importance of ensuring access to quality anti-infective medicines that a patient actually needs, while avoiding overuse. Consumption of anti-infective medicines when they are unnecessary fosters drug resistance and increases the need for different, more expensive products in the supply chain. This, as well as the increased absolute volume of tablets taken or injections given, in turn increases the potential reach of substandard or falsified products.

The example of widespread use of diazepam to treat malarial fevers given in the section "A case in point" illustrates how using inappropriate medicines can skew markets and open the door to falsified products. Successful efforts to limit irrational use of medicines will thus also lower the risk that poor quality medicines will reach patients. The promotion of the rational use of medicines – including access, dispensing practices and use at the patient level – is critical to maximizing the success of treatment as well as minimizing the risk of the development of antimicrobial resistance.

Supporting quality standards

Reducing access gaps and strengthening governance are important for preventing the production and sale of both falsified medical products and those that fail to meet quality standards. But the easiest way to guard specifically against substandard products reaching patients is to ensure that both manufacturers and distributors maintain consistently high technical standards.

WHO's Department of Essential Medicines and Health Products works with countries and expert committees to develop, implement and enforce standards that can deliver quality products across globalized supply chains, while taking into account local needs and conditions.[6] For example, they helped to develop the

testing methods for the contaminant levomethorphan, which proved so critical in the cough medicine case in Pakistan, Paraguay and beyond. This means not only providing support for standards development, but also building up the skills base for quality control, inspection and laboratory work. WHO works at global, regional and country levels to train regulatory staff in all of these areas.

Prequalification of manufacturers and laboratories

A core component of WHO's work to support good manufacturing practice is a system that certifies individual products made in a particular dosage by a given manufacturer, at a named site. The certification process is undertaken at the request of the manufacturer.

Known as prequalification, this process involves a stringent review of safety and efficacy data, as well as site inspections to ensure that good manufacturing protocols are in place, and the practices they outline are rigorously followed. WHO prequalification is a key marker of product quality, and can be very helpful to governments and other agencies that procure large quantities of medicines from other jurisdictions, where site inspections are not possible. Many global health organizations require that any medical products bought with funds they provide are prequalified by WHO.

Prequalification currently only covers medicines for HIV, tuberculosis and malaria; some reproductive health products; some vaccines and active pharmaceutical ingredients as well as in vitro diagnostic tests. Prequalification processes are available for a few antibiotics, notably those commonly used to treat opportunistic infections associated with HIV. Many antibiotics and other essential medicines, including several of those most commonly reported to the WHO substandard and falsified medical products surveillance database, are not yet covered by the prequalification process. The process does, however, exist for laboratories that are used for quality control and inspection of suspect medical products. As of July 2017, there were 45 prequalified laboratories globally, nine of them in sub-Saharan Africa.

Prequalification has an important secondary benefit. During the benchmarking and inspection processes, international technical teams work very closely both with production managers at local factories or laboratories, and with national regulators. Their hands-on involvement in this stringent quality assurance process contributes to developing production know-how and long-term capacity for effective regulation within a country.

In addition to the prequalification process, WHO's Department of Essential Medicines and Health Products provides ongoing guidance and support for the development and implementation of good manufacturing practices. This includes detailed documentation on quality standards for everything from water supplies to ventilation systems in production plants.[7]

Prequalified medical products, as well as other quality-assured products, are highly unlikely to be substandard when they leave the factory. However, as reports to the WHO GSMS database confirm, that does not mean they are not reported to WHO's surveillance database. There are two reasons for this. Firstly, prequalification greatly increases the marketability of a product, which makes prequalified medicines a tempting target for falsifiers. Secondly, although well-manufactured medicines are less likely to degrade than others, there is always the possibility that bad transport or storage conditions will impact upon a medicine's effectiveness. WHO's Department of Essential Medicines and Health Products has developed standards for good distribution practices to guide countries in developing and regulating transport and storage, but there is as yet no prequalification system for supply chains.

[6] The latest versions of most of these standards are published as annexes to the annual report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They can be accessed at http://www.who.int/medicines/services/expertcommittees/pharmprep

[7] A comprehensive list of available guidance can be found at http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/

5.2.2 Detection

Detecting substandard and falsified medical products requires a keen awareness of the likely risk factors (including product shortages), a culture that promotes the rapid exchange of information, and the technology and trained personnel to follow up suspicion with appropriate action.

Heightening awareness throughout the supply chain

When national authorities are aware of particular factors that might fuel the local market for medicines and other products that do not meet quality standards, they can detect problems more rapidly by focusing their surveillance efforts on areas of greatest risk. Stockouts and other product shortages should always raise a red flag; if regulators are made aware of these by health authorities or others, they can increase their vigilance around those products, both by collaborating with customs officials at ports and through surveillance of the supply chain and retail outlets.

The WHO global surveillance system helps to inform risk-based market surveillance and data collection in two ways. Firstly, it facilitates the exchange of information between countries, not least through the global network of focal points for substandard and falsified medical products. Focal point training usually brings together participants from the same geographical region, who often face similar challenges, and sometimes have to respond to the same substandard and falsified products, sold through a single interconnected network. The system fosters formal and informal connections that can be hugely helpful for the rapid exchange of the information that is needed to respond quickly when dangerous vaccines or medicines are discovered.

Secondly the system issues Rapid Alerts, which provides details of confirmed cases that might pose a public-health risk to another country, as described in Box 1. These alerts help to guide postmarket surveillance, and sometimes lead to the detection of more falsified products.

To take an example from west Africa, WHO issued a regional alert after a faith-based NGO in Cameroon reported falsified malaria medicines sold in bottles of 1000 tablets, branded with a WHO look-alike logo, apparently intended to give the product an aura of reliability. Nearby countries increased their inspections, looking out for large quantities of tablets packaged in plastic bottles bearing fictitious WHO logos (Fig. 22). Just two months later, in August 2013, Ghana reported that it had seized 64 000 doses of a similar product, which contained 2% of active ingredient.

This case is a victory for the surveillance system, but its sequel highlights a dilemma for regulators. Products labelled with the fake WHO logo continued to appear across west Africa for some time – in Liberia in March 2014, and in Niger the following September. Just over a year later, they were found in Mali. However, these medicines carried a quite different mark. It was still a fiction clearly derived from WHO's logo, but it was different enough from the previous versions to avoid arousing the suspicions of retailers who may have been warned about the earlier falsification. This provides another indication that those persons involved, like legitimate businesspeople, keep a close eye on market conditions, and on threats to their brands. Indeed, alerts issued by regulatory agencies have been found on laptops seized from people arrested for the falsification of medical products. While clear information about suspect products is important in protecting public health, regulators must also be wary of being too public with information that helps criminals to evade detection.

FIG. 22: FALSIFIED VERSIONS OF ANTIMALARIAL AND ANTIBIOTIC PRODUCTS DISPLAYING A WHO "ESSENTIAL DRUG(S) PROGRAMME" LOGO

Triangulating data: sharing information across systems

Unexpected and undesirable reactions to vaccines or medicines (referred to in medical circles as "adverse drug events" or "adverse events following immunization") can be a warning signal that the product is substandard or falsified. But substandard production and falsification are not the only reasons for adverse events or unexpected outcomes. Other types of surveillance can help to assess the likelihood that falsified or substandard medicines are actually at fault, and can help guide the best use of testing resources.

Pharmacovigilance systems, which track side-effects of medicines and other medical products, are the most important of these. While clinical trials try to quantify the safety of new medicines, side-effects may be missed because trials often last just a few months, and the number of participants is small compared to the hundreds of thousands who may go on to take the medicine over many years as patients. Some countries have well-developed monitoring and reporting systems that collect and collate information on adverse events related to medicines already in use. This information is analysed for patterns that may reveal side-effects that did not surface (or were not reported) in clinical trials.

A WHO collaborating centre, the Uppsala Monitoring Centre in Sweden, maintains a database of 15 million of these events. This provides information against which countries can cross-check suspect medicines, allowing them in some cases to rule out known or emerging side-effects as a possible cause of adverse reactions before further investigating medicine quality issues.

Although 110 countries currently report data to that database, some of that reporting is slow and much of it is incomplete – WHO estimates, for example, that two thirds of countries do not have a system that can adequately monitor adverse effects of vaccines once they are in the field. The WHO Safety and Vigilance Unit is working actively to strengthen pharmacovigilance and vaccine safety systems. This work should certainly heighten the awareness among health workers and improve the timeliness and completeness of reporting of adverse events. That, in turn, should contribute to regulators' ability to detect substandard and falsified medical products that have already harmed patients, and to respond appropriately.

One of the unexpected reactions to a medicine is no reaction at all: it simply has no effect on the patient. This is known as a lack of efficacy. In the case of infectious diseases, it may also be because the patient is infected with a strain of the pathogen that has developed resistance to the treatment.

WHO recognizes antimicrobial resistance as a major threat to health and welfare. However, in many countries, systems to track the spread of drug-resistant pathogens are entirely lacking. The Antimicrobial Resistance Secretariat at WHO and the Department of Essential Medicines and Health Products are thus working with partners around the world to strengthen surveillance for antimicrobial resistance. The data generated through the global antimicrobial resistance surveillance system and the GSMS for substandard and falsified medical products can help to assess the impact of substandard and falsified medical products on the emergence of antimicrobial resistance.

Improving detection technologies in the field and the laboratory

Detection is difficult, in part because sophisticated laboratory equipment is expensive to acquire and run, difficult to maintain and requires trained personnel who may be in short supply. A number of field detection technologies exist, but each has advantages and disadvantages and they are not always in the hands of people who have been trained to use them effectively (*47*).

WHO is coordinating with specialists from academic institutions such as the University of Oxford and technical bodies such as the United States Pharmacopeia to evaluate existing and emerging drug screening technologies that can be used at ports and in health care settings other than high-specification laboratories.

In addition, the WHO Substandard and Falsified Medical Products Group is supporting the development of new tools that will help front-line health care workers record and report suspect medicines – an important entry point for detection. Health care workers often identify a product that looks or smells wrong, or they find packaging that contains misspellings or unexpected expiry dates. All too commonly, they find that their patients are just not getting better.

Pharmacovigilance systems have been established in many countries to identify and monitor adverse reactions in patients who have taken medicines. These systems rely on reports from health care professionals or patients and carers to identify trends that may indicate a safety issue. It is possible to identify an unexpected lack of efficacy of a medicine in a patient, but there can be a number of reasons for this. When a medicine is not working, health care workers commonly switch patients to another one without reporting the incident. However, an unexpected lack of efficacy is a very important indicator that a product may be substandard or falsified. Health care workers sensitized to report such incidents can thus make an important contribution to detection. One example of this comes from Guinea-Bissau where, in 2013, community-based epilepsy services ran low on phenobarbital, a medicine used to prevent seizures. They restocked from a supplier who was offering very competitive prices. No one reported irregularities on the label (which included grammatical errors and the warning "Keep out of rech of children" (sic)). But when – within a month – they noticed that their patients were suffering epileptic seizures much more frequently than expected, they reported their suspicions. The tablets were brittle and varied substantially in weight. Their manufacturer was listed at a non-existent address in "Swipzeland", and laboratory testing showed that they contained virtually no active ingredient. Two years later, health workers in another west African country, Liberia, again noticed unexpected seizures in their patients. The tablets they had been giving patients were labelled with the same fictitious address, and included the same basic spelling mistake (Fig. 23). Again, they reported their concerns.

FIG. 23: FALSIFIED PHENOBARBITAL THAT WAS SUPPLIED TO A COMMUNITY HEALTH CENTRE

These health care professionals were vigilant and reported their suspicions. However, health workers do not always do this, for various reasons. Analysis of the accumulated data from the GSMS revealed that some of the most detailed and useful reports in the database were initiated by front-line health workers, who often kept samples to pass on to national regulatory authorities for testing. However, the overall proportion of cases initiated by health workers was low, at just 12%. WHO began to research ways to harness the suspicions of health workers and improve reporting, as a means of helping national regulators to increase detection of substandard and falsified products.

WHO worked with partners to develop a smartphone-based application specifically designed for health care workers who could take photographs of a suspicious medical product and send it to the regulator in under 90 seconds. Regulators would agree to respond to the report within 48 hours. That system has been piloted in the United Republic of Tanzania and is about to be piloted in south-east Asia. If the pilot study proves successful, wider roll-out of the application will be considered.

A CASE IN POINT

One case reported using the smartphone application to the Tanzania Food and Drugs Authority (TFDA) by a health care professional managing the procurement of medicines at a public hospital demonstrates the importance of training all health care professionals – from those procuring medicines to those administering treatment – in detecting substandard and falsified medical products.

In July 2017, a site visit to one of the health facilities participating in the smartphone application pilot trial was arranged in the United Republic of Tanzania. A group of experts from WHO and the TFDA met a health care professional who showed the team a box of used in vitro diagnostic kits for malaria that had delivered invalid results (Fig. 24). When the hospital staff tried to use a kit to test a patient for malaria, it would take multiple attempts to obtain a valid result. The hospital was using five diagnostic kits per patient and, as a result, stock ran out quickly and unusually large quantities of the kits were ordered. This raised the suspicions of the pharmacy procurement staff who reported it through the application. The TFDA took the opportunity to take samples of the kit for additional testing and a recall was subsequently issued.

FIG. 24: SUBSTANDARD IN VITRO DIAGNOSTIC KITS FOR MALARIA REPORTED VIA THE SMARTPHONE APPLICATION IN THE UNITED REPUBLIC OF TANZANIA

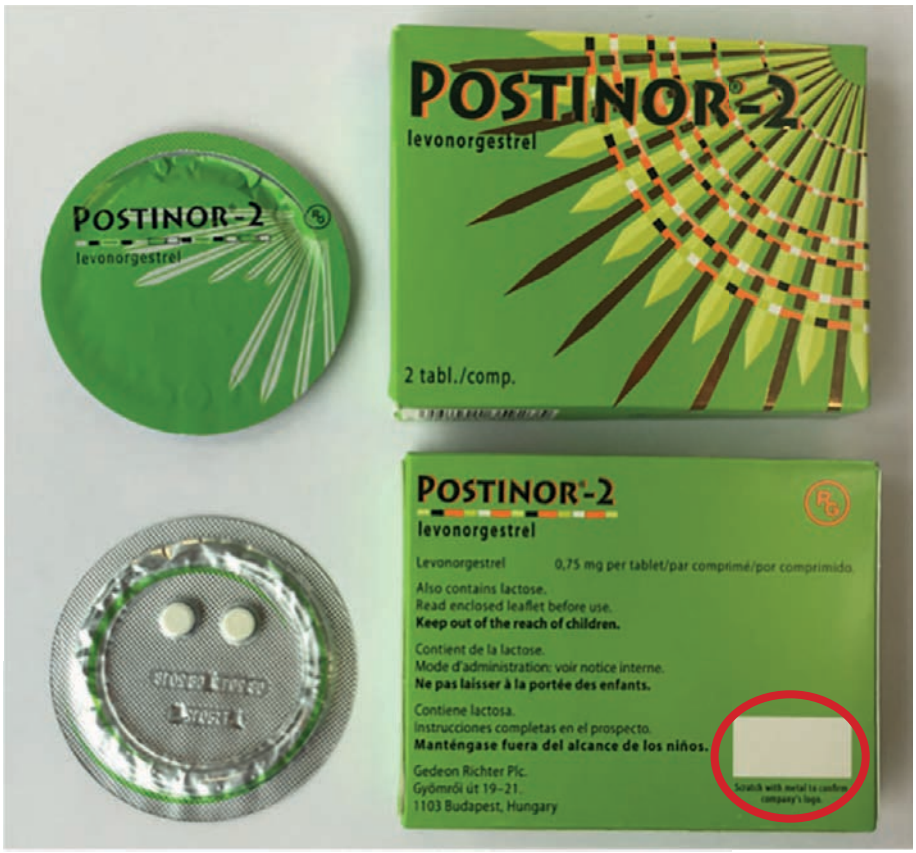
While tools can make reporting easier, they cannot overcome cultural barriers to reporting, including fear of reprisals. The WHO Substandard and Falsified Medical Products Group also works with national authorities to overcome possible disincentives to reporting, and to strengthen systems that protect and encourage people who use national systems to report suspicions and thus save lives.

Wider use of authentication technologies

While smartphone reporting technologies straddle the territories of detection and response, other technologies deal with prevention and detection. These include track and trace technologies, which allow for the seamless tracking of products through the supply chain, and authentication technologies, which allow legitimate products to be distinguished more easily from falsified products.

This sort of authentication technology allowed the Ugandan national regulatory authority to identify falsified contraceptives. Although the falsifiers had included a greyed-out area on the fake packaging that imitated a scratch-off authentication device, it was not actually scratchable (Fig. 25). This alerted inspectors to the likelihood that the tablets were not genuine, a fact later confirmed both by the manufacturer of the original product, and by laboratory analyses, which found no active ingredient.

FIG. 25: FALSIFIED EMERGENCY CONTRACEPTIVE WITH FALSIFIED AUTHENTICATION DISPLAYED



The Member State mechanism on substandard and falsified medical products has taken the lead on coordinating work in this area. Guided by Argentina, a technical working group undertook a comprehensive review of the overt and covert authentication systems that legitimate manufacturers can use in marking their products. The working group also reviewed the track and trace mechanisms that allow for the more rapid detection of falsified products in the supply chain (*48,49*).

5.2.3 Response

Much of the necessary work on response falls into the area of governance. The need for effective, transparent regulation, and strong institutions to implement it, is apparent in almost every one of the cases discussed in this report. WHO's Regulatory Systems Strengthening team works with national regulatory agencies to develop or strengthen the procedures and skills needed to keep a country's supply of medical products safe and effective.

To tailor its support to a country's needs, WHO has developed an assessment tool that countries can use to compare their systems and resources with international quality benchmarks. The group provides help with this assessment process when requested, and will also work with governments to strengthen systems and standards.

Globalized manufacturing processes and supply chains combined with fragmented national markets present a particular challenge for governance systems related to medical products. National regulators have seen the scope of their work expand, while international regulatory systems remain underdeveloped. Without more investment, regulatory systems will not be able to keep pace with globalization. The Regulatory Systems Strengthening team therefore also works with national and regional institutions to develop harmonized regulations that reduce duplication, are proportionate to current circumstances, and lighten the load of individual national regulators. They also support the sharing of knowledge, skills and systems at the regional level.

As new structures and norms of governance evolve, it will be important to ensure that regulators have the political support, the resources and the legal framework they need to coordinate and implement activities that detect and respond to substandard and falsified medical products in the supply chain, to prevent future occurrences and to protect public health.

Alert versus alarm

On a more technical level, systems for reporting and communication form a core part of an effective response when suspect products do enter the supply chain.

The network of nationally designated focal points for substandard and falsified medical products, and their interaction with surveillance staff in Geneva, are becoming crucial to a reporting system that meets the needs of today's complex landscape. Officially nominated national focal points have access to a secure portal through which they can submit core information about suspected cases directly to the database using standardized online forms. Supplementary information is entered as it emerges by analysts in Geneva, who classify the case by type (substandard, falsified, unregistered or unknown). Official focal points can also consult the database using product and manufacturer names, as well as batch numbers if available, to see whether there have been any similar reports from other countries or regions that might help indicate the provenance or composition of a suspect product, or otherwise guide further investigation.

The cross-referencing system within the GSMS database allowed for the rapid identification of the toxic cough syrup in Paraguay, mentioned at the start of this report, and led to the seizure of medicines before they reached the market in other countries. In other words, cross-checking helps countries respond, while also preventing harm.

If a previous case has been confirmed, focal points will be able to see details, including where and when it occurred, accompanied by photographs of the product in question, when available. For unconfirmed cases, or if they have additional queries, they are invited to contact database managers for more details. In most cases, focal points interact extensively with WHO staff in Geneva, providing details of cases and receiving feedback and support as necessary. In rare cases where WHO receives a report through channels other than a focal point (for example, from a patient, or from a pharmaceutical company), the group will immediately inform the focal point in the countries in question for follow-up and confirmation. If a report from any source involves a medical product suspected of seriously harming patients, the group will follow up within 24 hours to arrange with focal points any extra support and assistance they need. Less threatening cases are followed up within 72 hours.

If a case reported to the WHO surveillance database is confirmed and judged to have potential implications

for other countries, WHO staff will discuss with focal points the possibility of issuing a regional or a global alert.[8] Such alerts are publicly available, but are also actively distributed to all relevant national medicines quality focal points and their colleagues in WHO country and regional offices, so that they can be brought rapidly to the attention of national regulators.

One of the most difficult aspects raised by the threat of substandard and falsified medical products is public communication. On the one hand, authorities want citizens to be alert all the time, and governments must certainly provide information when substandard or falsified products that threaten health might have reached patients. On the other hand, they want to avoid alarming patients and the public, and they certainly do not want to undermine confidence in medical services. There is some danger, too, that providing very comprehensive information can help falsifiers to circumvent response measures. The Member State mechanism, led in this instance by the United Kingdom, is developing guidance that aims to help authorities to achieve the right balance when communicating information about quality concerns relating to medical products in the market.

Technical support for investigation

Countries that have limited experience with investigation may request support for following up suspected cases. The Substandard and Falsified Medical Products Group can help put national investigators in touch with key contacts in the reported manufacturing company of a suspect product, or if the manufacturer is unrecognized – with the regulator in the reported country of manufacture.

The group in Geneva can also provide advice on the most appropriate testing methods and technologies. Where local laboratories do not have the capacity to carry out the necessary tests, surveillance system staff can facilitate testing in a quality-assured laboratory in another country. In very complex investigations, regulators can request on-site help from technical experts based in Geneva.

5.2.4 Implementation: coordinated national plans

The whole cycle of prevention, detection and response relies heavily on effective coordination between the many different actors who have parts to play in assuring that medical products are of reliable quality. The Member State mechanism has begun that task of coordination at the global level. At the national level, an effective, fully resourced national action plan, which lays out roles, responsibilities and actions, is a very useful starting point.

A Member State mechanism working group led by Brazil has developed straightforward guidance that will help countries develop and strengthen the institutional framework and procedures necessary to curb production and sale of substandard and falsified medical products.[9] Taking the Prevent, Detect, Respond approach, it provides detailed examples of actions required to achieve those higher-level goals (Table 4).

Once robust coordination mechanisms have been put in place, a national plan developed and resources secured, the major challenges will revolve around reinforcing and deploying the capacities needed to implement that plan. This is in itself a governance challenge. To help track progress towards this goal, Table 4 provides examples of elements to include in a national action plan.

[8] Alerts are issued only if a case has been adequately verified (for example through laboratory analysis), where it is likely that the product remains in circulation, and where it may pose a public health threat to consumers in other countries. More details of these criteria can be found at http://www.who.int/medicines/regulation/ssffc/medical-products/en/

[9] http://www.who.int/medicines/regulation/ssffc/mechanism/A70_23-en6-14.pdf?ua=1, accessed 13 October 2017.

TABLE 4: EXAMPLES OF ACTIONS TO IMPLEMENT THE PREVENT, DETECT, RESPOND APPROACH

PREVENTION	
Education and awareness	There are focused education, media and awareness programmes, for non-health professionals, the general public and civil society groups on substandard and falsified medical products.
	The issue of substandard and falsified medical products is integrated as part of the core medical, pharmacy and regulatory curriculum.
Comprehensive legal framework	There are legal provisions in place enabling the national medicines regulatory authority (NMRA) to seize, quarantine, sample, analyse, recall and destroy substandard and falsified medical products.
	There are legal provisions in place for the inspection, investigation, enforcement and proportionate sanctioning of those engaged in the manufacture, distribution, storage, supply and sale of substandard and falsified medical products.
	There is a documented strategy and guidelines in place and implemented relating to the prevention, detection and response to substandard and falsified medical products.
Multistakeholder engagement	There is clear and regular communication with civil society groups, health care professional organizations, the pharmaceutical industry and actors within the supply chain, specifically focusing on substandard and falsified medical products.
	There are documented and implemented procedures for regular engagement with the relevant government departments and agencies, including national pharmacovigilance centres, national poison centres and national quality control laboratories.
Supply chain integrity	A track and trace system with an authentication process has been implemented for medical products.
	The supply chain has been mapped from point of manufacture or importation through to public outlets, pinch points identified and staff trained to identify, report and respond to suspected substandard and falsified medical products.
DETECTION	
Border control	There are designated ports for the importation and export of medical products, and a regulatory presence at those ports.
	There are documented and implemented procedures for allowing the exchange of information concerning suspected substandard and falsified medical products between customs, police and the regulatory agency.
Reporting systems	Effective public reporting systems exist, enabling the reporting of suspected substandard and falsified medical products and adverse drug reactions to the NMRA.
Risk-based inspection and surveillance	A risk-based strategy is documented and implemented for conducting regular targeted and random market surveillance for substandard and falsified medical products within the regulated and unregulated supply chains.
	There is a documented and implemented risk-based inspection programme for those entities engaged in the manufacture (including relabelling/repackaging), importation, distribution/wholesale and supply/sale of medical products.
Access to laboratories and screening technologies	There is access to an externally accredited national quality control laboratory and documented procedures are in place and implemented regarding the analysis and reporting of substandard and falsified medical products.
	There is access to field screening equipment (and relevant reference material), which staff have been trained to use, and procedures are documented and implemented for the use of such equipment.

RESPONSE	
Alerts and recalls	A documented and implemented procedure exists concerning the issuing, receipt and response to Rapid Alerts concerning substandard and falsified medical products.
	A designated and trained focal point(s) within the NMRA has been established to receive and respond to reports of suspected substandard and falsified medical products and has access to the WHO Global Surveillance and Monitoring System for substandard and falsified medical products.
Regulatory strengthening	Regulatory personnel are designated and trained in the response to substandard and falsified medical products and documented procedures have been established and implemented.
	The prevention, detection and response to substandard and falsified medical products has been embedded in core regulatory responsibilities across departments and government agencies and is included in regulatory assessment indicators.
Transparent legal process	The use of regulatory or criminal law sanctions is justified and applied in a consistent and proportionate way. The application and use of sanctions is published by the national or regional regulatory authority.
Evidence-based policy and procedure	Each incident involving substandard and falsified medical products has been reviewed with a view to identifying weaknesses in the system, vulnerabilities in the supply chain and making appropriate changes to improve the safety of patients.
	There is clear use of data from a wide range of sources in developing evidence-based policy and procedures to prevent, detect and respond to substandard and falsified medical products.

Regional plans

For countries to be successful in addressing substandard and falsified medical products they need to be well organized and resourced at the national level and well connected to the relevant stakeholders with communication channels open and effective.

But there is also a need to be equally well connected with neighbouring countries, particularly those with which borders are shared or that share regional economic areas. Rapid sharing of information is important and the establishment of mechanisms to achieve this are an example of good practice. Very effective regional systems have been established in Latin America, western Europe and some parts of south-east Asia with others emerging in parts of Africa. A number of areas have established regional rapid alert systems. Strong regional partnerships between countries, with established groups comprising practitioners, have proved very successful in some parts of the world.

But, as mentioned previously, the trade in medicines and vaccines and their active ingredients is now truly global. Globalized trade needs global surveillance. An integrated approach from the national, regional and global level is now crucial to protect patients in all of our countries.

6. CONCLUSION

The world is changing rapidly. Advances in technology, a step-change in communications and access to information, low-cost transport and the growth of huge, transnational corporations are all reshaping the global landscape, powerfully affecting everyone's lives. The quality of medicines and medical products is one of the many things touched by these forces.

The nearly 1500 cases reported to the WHO GSMS over its first four years of operation provide many very graphic examples of how global changes contribute to the production and trade in medicines and other products that fail to meet quality standards. Although they represent only a fraction of the true number of suspect products in circulation, these cases are already increasing knowledge of the forces that underpin and facilitate the manufacture, sale and distribution of substandard and falsified medical products. An increased understanding of these patterns of risk leads to a greater ability to prevent, detect and respond to those risks. That understanding depends on the active exchange of information through robust systems maintained by a neutral and trusted agency, and on the rapid analysis and appropriate communication of that information to those who can act on it.

Effective global coordination mechanisms like the Member State mechanism now exist, and are growing ever stronger. Global institutions, including WHO, are working in broad partnerships on many fronts to support the development of the systems, workforce, tools and skills that are needed. The world has never been better equipped to tackle the problem of substandard and falsified medical products. If governments and other decision-makers sustain these efforts and resource them appropriately, it will be possible to turn back the rising tide of falsification, increase quality standards globally, and ensure that people all around the world have reliable access to medical products that work as they are supposed to.

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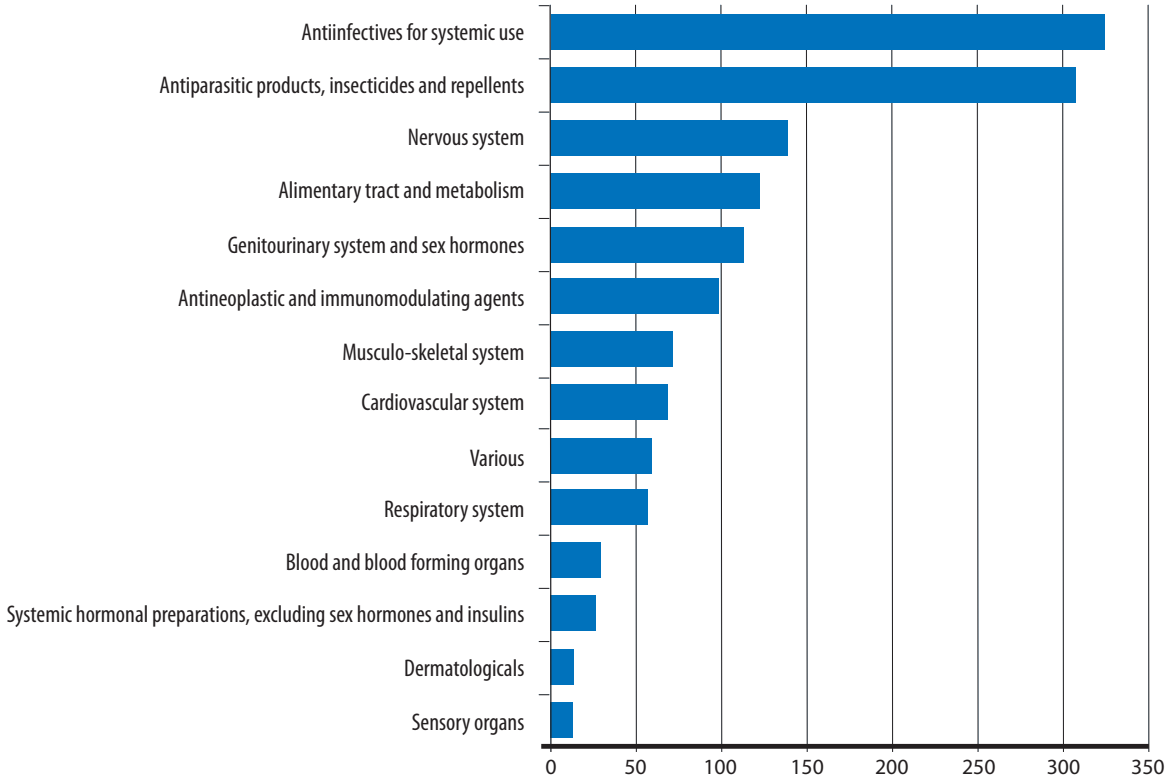
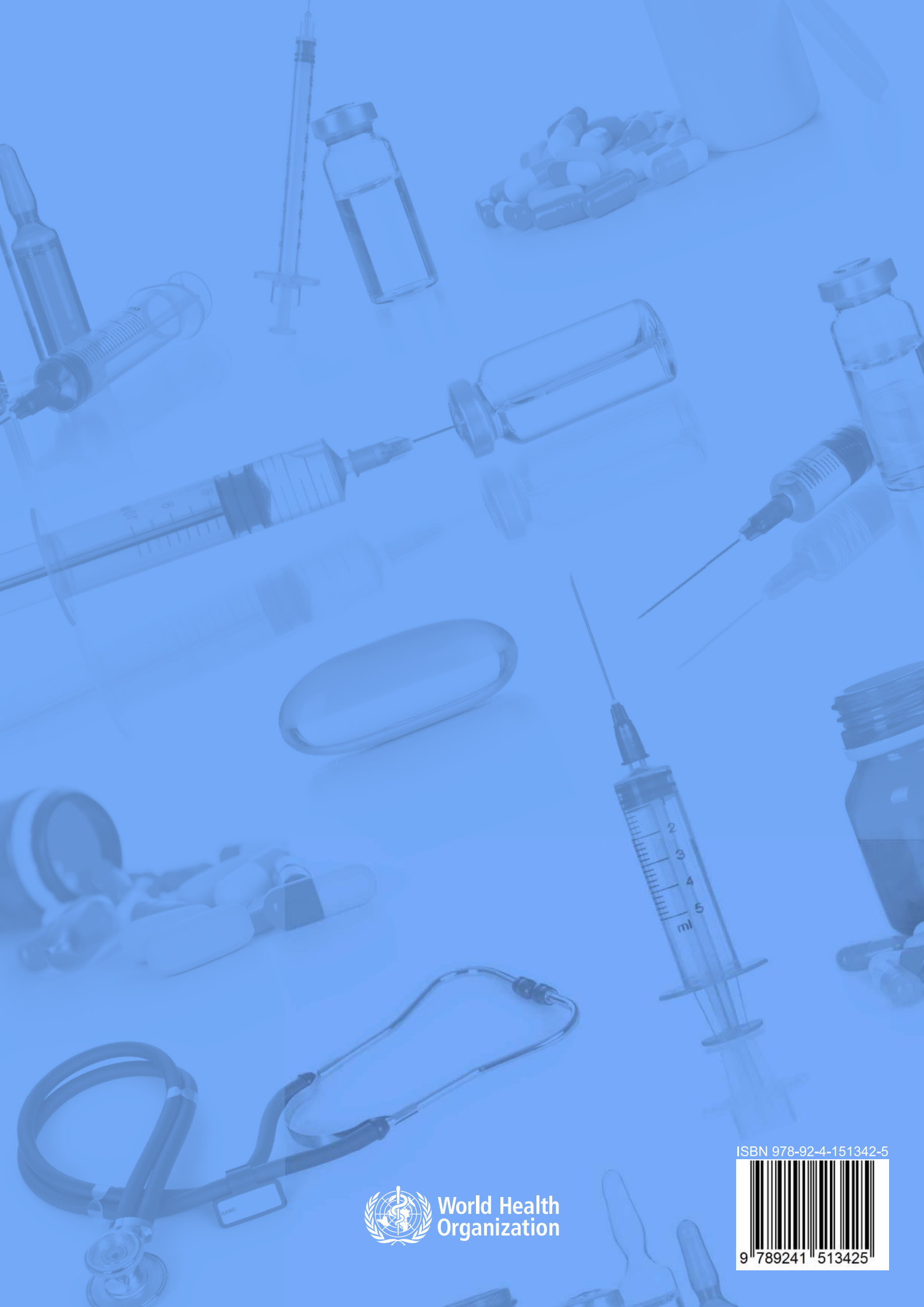
ANNEX

Reports to the WHO GSMS based on Anatomical Therapeutic Chemical (ATC) classification system (2013-2017)





ISBN 978-92-4-151342-5

World Health Organization