# Trade in substandard and falsified medicines

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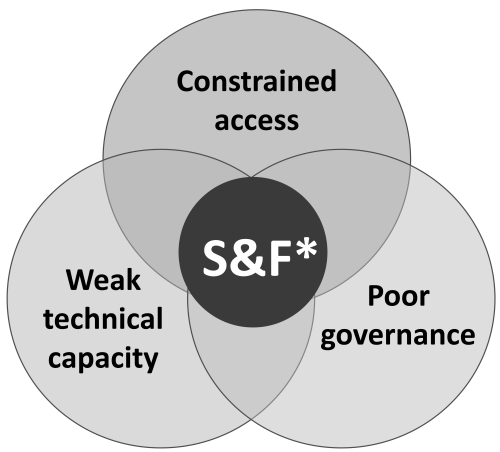
## *Introduction*

The spread of substandard and falsified (SF) medicines is one of the most urgent health challenges of our time. In 2017, the World Health Organization (WHO) estimated that 1 in 10 medicines in low- and middle-income countries (LMICs) is substandard or falsified. Constrained access to medicines through the legal supply chain, low standards of governance with regard to medicine regulation and weak technical capacities e.g. in national medicine quality control laboratories are related to a high prevalence of SF medicines (Fig. 1) (WHO 2017a).

*Figure 1: Factors that contribute to the emergence of substandard and falsified medical products. Modified from: WHO (2017a).*




**S&F*: substandard and falsified medical products**

About one third of the world's population lacks access to medicines, vaccines and other essential health products (WHO 2020a). To achieve universal health coverage, which is part of Sustainable Development Goal

3 of the United Nations (UN), equitable access to safe, effective, quality and affordable essential medicines and vaccines (target 3.8) is of key importance. SF medicines pose a serious threat not only to public health but also to family and government budgets by prolonging or even causing illness and hospitalisation, in addition to loss of wages. They undermine trust in health services and contribute to the emergence of drug-resistant pathogens. The growing complexity of supply chains in our globalised world and the increasing popularity of e-commerce provide numerous entry points for illegal medical products. Even trained professionals often have difficulties to detect SF medicines, and if detected these products are often not reported (WHO 2017a).

According to the International Criminal Police Organization (INTERPOL), the trade in falsified medicines may have become more attractive to organised criminal networks than trafficking in illegal drugs due to high profits, a very low risk of detection and prosecution as well as penalties that are small compared to the penalties for illegal drug trafficking (INTERPOL 2014). The profits made with falsified medical products may also become a resource to fund other types of illegal activities (INTERPOL 2014; WHO 2017a). The outbreak of the COVID-19 pandemic led to a worldwide increase of SF medical products as criminals took advantage of the high demand for personal protection and hygiene products, medicines and vaccines (INTERPOL 2020a).

### *Definition of substandard and falsified medicines*

To understand and address the problem of substandard and falsified medicines, a common understanding of their definitions is crucial. After many years of controversy, the World Health Assembly of 2017 finally introduced an authoritative definition of substandard and falsified medicines (WHO 2017b).

"Substandard" refers to authorised medical products that fail to meet either their quality standards or their specifications, or both. "Falsified" medical products deliberately or fraudulently misrepresent their identity, composition or source. These definitions are mutually exclusive, and samples can either be classified as substandard or as falsified (WHO 2017b; UNODC 2019).

"Substandard" medicines may result from unintentional shortcomings in the manufacturing of the products and/or from deterioration occurring after manufacturing. Medicines that are sensitive to high temperatures and humidity can easily become "substandard" e.g. if subjected to poor trans-

port and/or poor storage conditions. However, the stability of medicines depends not only on storage conditions but also on the formulation of the products, e.g. on the choice of excipients and stabilising agents. Therefore, the manufacturing procedures as well as the packaging play a crucial role for the stability of medicines.

A product is considered not as "substandard" but as "falsified" if an authorised manufacturer deliberately fails to meet the quality standards or specifications due to misrepresentation of identity, composition or source (WHO 2017b). Obviously, however, it is not always possible to obtain information on the intention of the manufacturer, and chemical analysis for the identity and quantity of the active pharmaceutical ingredient (API), as well as additional pharmacopeial analyses like dissolution testing, are not sufficient to unequivocally classify a medical product as substandard or as falsified. Packaging inspection and requests to the manufacturers and distributors for authentication of the products in question can be helpful to obtain additional information (Hauk, Hagen and Heide 2021).

The term "counterfeit" has been used as a synonym for falsified medical products, or even for "poor-quality" medical products in general. However, the term "counterfeit" should only be used for products that infringe on registered trademarks or intellectual property rights, and this term is no longer used in the WHO definitions. WHO tries to focus on public health problems and not on the protection of trademarks and intellectual property rights. Therefore, the terms "trademark counterfeit goods" and "pirated copyright goods" are defined under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (WHO 2017b).

Previously, the United Nations Office on Drugs and Crime (UNODC) used the terms "fraudulent medicines" and "falsified medicines" interchangeably (UNODC 2011). However, in its 2019 guide on "Combating falsified medical product-related crime", UNODC now also adopted the recent WHO terminology and uses the term "falsified medical products" (UNODC 2019).

Concerning the definition of "substandard" medicines, it should be noted that the tolerance limits for acceptable deviations, e.g. of the actual content of the API from the declared content, may vary between different pharmacopoeias, e.g. the International Pharmacopoeia, the United States Pharmacopeia or the British Pharmacopoeia. Therefore, a given product may be "in specification" under the criteria of one pharmacopoeia, and "out of specification" under the criteria of another one. This may quite strongly influence the prevalence rates of "substandard" medicines reported in different medicine quality studies, even more so as some studies use

arbitrary rather than pharmacopeial tolerance limits (WHO 2017c; Hauk, Hagen and Heide 2021).

### *Prevalence of substandard and falsified medicines*

From a review of one hundred scientific studies published between 2007 and 2016 and selected for their scientific quality by an Expert Working Group, WHO estimated that around 10.5 % of the medicines in LMICs are substandard or falsified (WHO 2017c). However, the reported prevalence data vary strongly between different studies, and reliable estimates on the prevalence for different regions, for different parts of the supply chain and for different types of medicine are still urgently needed. Systematic reviews of medicine quality studies by Ozawa et al. (2018), Almuzaini, Choonara, and Sammons (2013) and McManus and Naughton (2020) reported prevalences of SF medicines between 13.6 % and 28.5 % in LMICs. Notably, none of these studies was able to differentiate substandard medicines from falsified medicines, due to the heterogeneity of methodologies and definitions used in the reviewed studies. Guidelines and checklists for the conduct of medicine quality studies have been published and may help to reduce the heterogeneity of methodologies in future (Hauk, Hagen and Heide 2021; WHO 2016; Newton et al. 2009).

To gather more information on the magnitude of the problem, WHO launched a Global Surveillance and Monitoring Systems (GSMS) Portal (WHO 2021d). National medicines regulatory authorities (NMRAs) can report suspect medical products to this portal and check if similar products have been found elsewhere. 1,500 reports of SF medical products were submitted to WHO between 2013 and 2017. Antimalarials and antibiotics seem to be the most affected therapeutic classes, according to the number of reports (19.6 % and 16.9 % of the overall reports, respectively) and the prevalence rates in published studies. Most of the reports to the GSMS portal come from the WHO African Region (42 %). However, this does not mean that other regions and therapeutic classes are not affected. The GSMS database shows that all types of medical products, from cancer medicines to contraceptives and painkillers, including branded as well as generic products, expensive as well as cheap medicines, and all regions of the world are affected by the problem of SF medicines (WHO 2017a). Reports on negative health impacts caused by falsified medicines also come from high-income countries and concern falsified sedatives, hypnotics, narcotics and medicines for sexual dysfunction (Rahman et al. 2018). The rising number of substandard and falsified medical products in times of the

COVID-19 pandemic impressively shows how constrained access through the legal supply chain is linked to an increase in the number of SF products (Van Assche, Caillet and Newton 2021a).

### *Impact of substandard and falsified medicines*

SF medicines have a multidimensional impact on public health as well as severe economic and socioeconomic consequences, and they thereby impede the achievement of the Sustainable Development Goals. Death by intoxication or other serious health consequences resulting from SF medicines that contain the wrong API or toxic chemicals are among the most serious health impacts on the individual patient. Much more frequently, SF medicines which lack the correct API, or contain an insufficient amount of the API, lead to treatment failures resulting in prolonged morbidity, disease progression and even death (WHO 2017c). Only few reports of SF medicines have attracted worldwide attention, such as the death of children from acute kidney failure due to toxic diethylene glycol in teething syrup in Nigeria (Akuse et al. 2012) or the hospitalisation of 930 patients (11 of whom died, including 5 children under five years of age) due to an intentional mislabelling of haloperidol tablets as diazepam tablets in the Democratic Republic of Congo (Peyraud et al. 2017). WHO estimated that every year treatment failures resulting from SF medicines lead to the death of 72,000 to 169,000 children with pneumonia worldwide and to the death of 31,000 to 116,000 patients from malaria in Sub-Saharan Africa alone (WHO 2017c). Treatment with SF antimicrobials may also lead to an increase of antimicrobial resistances. For example, the use of SF antimalarials containing only subtherapeutic doses of the active ingredients was associated with increases in the resistance to antimalarials in several studies (WHO 2017c). Furthermore, founded or unfounded reports about the occurrence of SF medicines can lead to mistrust of patients towards medications and the health system in general, resulting in underutilisation of health facilities, non-adherence to prescribed treatments and vaccine hesitancy.

Spending money on ineffective or harmful medicine is a waste of economic resources. SF medicines also lead to additional costs in the long term. Treatment of prolonged illness, adverse reactions, drug-resistant infections and infections resulting from failed prophylaxis strain the limited budget of health systems and health insurance companies. Especially in LMICs, where the share of „out-of-pocket" payments of the total current health expenditures is still high (37 %, compared to 14 % in high-income countries),

this can lead to financial hardship for individuals and their families (WHO 2017c). Additional health interventions required due to treatment failure of SF antimalarials are estimated to cost between US$12.1 million and US$44.7 million annually (WHO 2017c). Lost productivity and income, lack of social mobility and increased poverty are among the socioeconomic impacts of SF medicines.

For legitimate manufacturers, counterfeit and falsified medicines mean lost sales and costs for brand protection and may lead to a loss of reputation. In the European Union, this results in an estimated €10 billion of lost sales annually (OECD and EUIPO 2020; EUIPO 2020).

### *Licit and illicit flows through complex supply chains*

In 2020, two-thirds of the APIs used to manufacture generic medicines for the European market were produced in Asia (Progenerika 2020). APIs, excipients and packaging material are often produced in different countries and shipped to the place where the finished pharmaceutical product is produced, which may then be packaged in yet another country. Also, the subsequent supply chains are highly complex, and the medicines are often traded through several distributors situated in different continents and countries before they reach the health facility and patient (Hauk, Hagen and Heide 2021). Long and complicated routes and repeated repackaging by distributors and wholesalers make it easy for criminals to introduce substandard or falsified products into the legal supply chain. Especially wholesalers represent an entry point for falsifications, as licit and illicit flows can easily mix here, with or without intention by the wholesaler. This is exemplified by the Avastin® case described below. As a result, substandard and falsified medicines can be found in the legal supply chain, although their prevalence is higher on the black market (Buckley and Gostin 2013; Schäfermann et al. 2020).

Today, originator medicines (i.e. innovator products, usually protected by patents) represent only a minor part of the medications used, while the vast majority of patients is treated with generic medicines. In the US, only one out of ten prescriptions filled are for originator medicines, the rest are generics (FDA 2021). Many LMICs rely on imports of medical products. In some African countries, these account for more than 80 % of the medicines available in the country, and most of these are generics (Byaruhanga 2020). This is exemplified by a study on substandard and falsified medicines in Cameroon and the Democratic Republic of Congo: of the 502 samples investigated, 71 % were manufactured in Asia (mostly in India and China)

and less than 3 % in the African country where the sample was collected. Only 6 % were originator medicines (Schäfermann et al. 2020).

Not only most of the legitimate medical products are manufactured in India and China, but also drug precursors and falsified products have been reported to come from these countries (UNODC 2010; INCB 2018). A total of 363 production places for falsified medicines were shut down by the Chinese government in 2008 (People's Daily Online 2009). Illegal distributors in Africa are often directly connected with criminal manufacturers in India or China. In these cases, illegal products, often containerised and falsely declared to avoid inspections, are shipped out through regular freight companies, but also through other distribution channels by specialised couriers (UNODC 2010).

Especially in LMICs, the supply chain is extremely fragmented and includes public, private and NGO distribution systems and specific donor-funded medicine procurement for HIV/AIDS, malaria, tuberculosis, vaccines and reproductive health programmes. These multiple parallel distribution systems and the lack of national coordination mechanisms make it difficult to control and plan procurement and distribution of medicines within a country (Yadav, Tata and Babaley 2011).

### *Trafficking of substandard and falsified medicines by informal networks, organised crime groups and terrorist organisations*

As noticed by the UN Commission on Crime Prevention and Criminal Justice (CCPCJ), organised criminal groups (OCGs) are involved in all aspects of trafficking in SF medicines (UNODC 2011). But informal networks also play an important role, often centering around business partners, families or friends (Hall, Koenraadt and Antonopoulos 2017). According to INTERPOL, the size of the OCGs involved ranges from small clusters of three to ten persons up to larger groups that are well-established, hierarchical and sophisticated, often international (INTERPOL 2014). It is assumed that these OCGs as well as the informal networks use the same routes and techniques as they use for trafficking other illicit goods. They often operate in both licit and illicit circles, both globally and locally, and both online and offline. Especially the use of illicit online pharmacies has increased in recent years (INTERPOL 2021b, 2014). On the other hand, the use of legitimate companies that serve as a shield for criminal activities and allow OCGs and informal networks to expand their network and launder profits is also common (OECD and EUIPO 2020; INTERPOL 2014). Often, these OCGs and informal networks use

new technologies and platforms such as the darknet for trafficking SF medicines and to avoid getting caught by law enforcement authorities (Hall, Koenraadt and Antonopoulos 2017; Europol 2021). In a pan-European operation supported by Europol in October 2019, six OCGs were disrupted and 48 suspects were arrested. During the operation, 34.5 million units of medicines and doping products worth €2.6 million were seized (Europol 2020).

Terrorist groups are also linked to trafficking SF medicines. One example is the Irish Republican Army (IRA), who falsified veterinary medicines (Ivomec® from Merck) to finance their activities in the 1990s. The falsified medicines were produced by IRA members in the US. They contained no API and were distributed through a subsidiary of a large distributor. The scam was discovered by Merck, who sued the distributor and the individuals involved (UNIFAB 2016; IRACM and Przyswa 2013).

The Lebanese Hezbollah is also frequently linked to the trade with SF medicines. In 2006, an international network with activities in Lebanon, Canada, China, Brazil, Paraguay and the US was busted by the US Terrorism Joint Force. The network had been involved in the trade of SF medicines for sexual disorders. According to documents found, some of the profits were used to fund Hezbollah (IRACM and Przyswa 2013).

### *Non-medical use of pharmaceuticals: the example of tramadol and Captagon® (fenetylline)*

The non-medical (mis-)use of the painkiller tramadol has led to a veritable "tramadol crisis" in West Africa and the Middle East (Klein 2019; UNODC 2021a). The synthetic opioid tramadol is misused for its calming and euphoric effects and to overcome tiredness. With prolonged use, it may cause addiction, serious health damage and even death (UNODC 2021a). In countries influenced by Islamic laws and norms, alcohol and illegal drugs are often considered inacceptable, and consumption of substances with a medical appearance, such as tramadol, may offer a socially acceptable alternative (BBC 2018). Reportedly, in Egypt around 20 % of the male university students use tramadol and 60 % of these suffer from drug-related problems (Bassiony et al. 2018).

Tramadol is not under international control and therefore relatively easily available even in countries where it is on national control lists, such as Niger and Nigeria, as neighbouring states with lower levels of regulation can be used as entry points for illegal imports (UNODC 2021a). Internationally controlled substances are listed in the schedules annexed to the

three UN Conventions of 1961, 1971 and 1988 on narcotic drugs and psychotropic substances and need an authorisation of the importing state to enter the country (UNODC 2021b). Governments have to estimate the quantities required for legitimate purposes beforehand to restrict the use and trade in such substances and to ensure adequate supply for medical and scientific purposes (UNODC 2021a; INCB and WHO 2012). The main source of misused tramadol tablets – often higher dosed than products which are legally available – is the illicit pharmaceutical market that is supplied by criminal networks. However, the legal and illegal sectors overlap at many points of the supply chain, and there are indications that large amounts of tramadol which had been legally produced and exported were diverted into illicit channels and smuggled across countries (UNODC 2021a). This problem afflicts many countries in Africa and the Middle East (INCB 2019). Most of the illicit tramadol is transported from South Asia via maritime routes to West African ports. For example, 87 % of the tramadol seized in Ghana in 2017 originated in India (UNODC 2021a). Both hierarchical and loose networks are involved in the trade (UNODC 2021a). According to INTERPOL, terrorist groups are also involved and may use this as a source of finance (INTERPOL 2020c).

In 2017, more than 92 tons of tramadol were seized in Nigeria (UNODC 2021a). To combat the illicit trafficking, India changed its legislation on tramadol in April 2018, placing the export of this substance under the regulations for controlled drugs. Indeed, the amount of tramadol seized in Nigeria decreased to about 22 tons in 2018, and its price on the informal market increased, demonstrating the effectiveness of India's intervention (UNODC 2021a). However, putting tramadol under international control, as requested e.g. by the Egyptian government, may impair the availability, accessibility and affordability of this essential analgesic for medical purposes, especially in LMICs and in humanitarian relief efforts (Klein 2019). Moreover, criminal networks may replace tramadol with other opioids, such as tapentadol, which is already being used by opioid addicts in India and West Africa (UNODC 2021a; Basu et al. 2020).

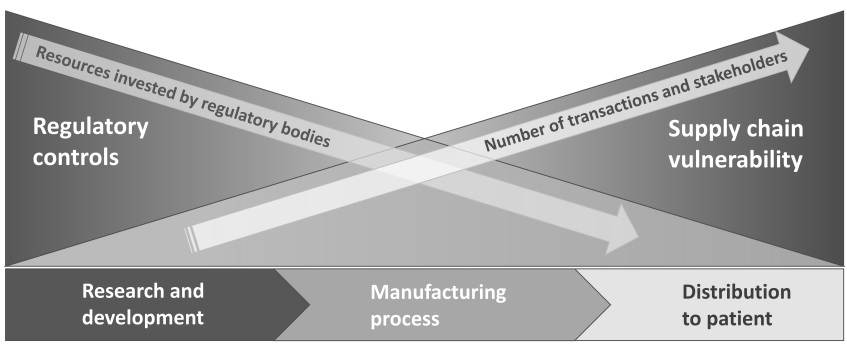
A connection between terrorist groups in the Middle East, terrorist attacks in Europe and the trade of the medical product Captagon® was suggested by several lay media reports. However, evidence is limited and further investigations, in particular forensic analysis, are necessary. In the 1960s, Captagon® with fenetylline, an amphetamine derivative, as the API was used e.g. for attention deficit disorder, mainly in Europe and the Middle East. After its declaration as a psychotropic substance by the UN Commission on Narcotic Drugs in 1986, the production and use of Captagon® was prohibited in most countries and legal manufacturing

stopped worldwide in 2009. It is assumed that until the end of the 1990s genuine Captagon® tablets were diverted from European stocks for illicit sale, mainly in the Middle East and in some countries bordering the European Union. Subsequently, tablets bearing the distinctive Captagon® logo of two half-circles but containing different types and quantities of amphetamine derivatives and referred to as "Captagon", which were reportedly commonly used as a stimulant in these countries, emerged amongst the seizures. Although evidence is sparse, it is assumed that most of this falsified "Captagon" was illicitly produced in the Balkan region, with a shift to Middle Eastern production beginning in the mid-2000s (EMCDDA 2018).

*Weak regulation favours trafficking of substandard and falsified medicines*

Regulatory controls are strong, with corresponding high investment of resources, at the early stages of the medicine supply chain, which includes e.g. the regulation of clinical studies and the licencing of pharmaceutical products. Conversely, at the end of the supply chain, when the medicine reaches the patient, these controls are much weaker, and the resources invested are much more limited. The supply chain vulnerability increases thereby, and this is exacerbated by the increasing number of transactions and stakeholders involved (Fig. 2) (WHO 2017a).

*Figure 2: Correlation between regulatory controls and supply chain vulnerability at different points of the supply chain. Modified from: WHO (2017a).*



The quality of medical products made for export is often regulated much more poorly than that of those which are licensed for domestic marketing (Bate et al. 2014). The consequences of this poor regulation are aggravated by the fact that in many LMICs the NMRAs are weak and lack the capacity to thoroughly assess the quality of imported medicines before registration. Sometimes, it is even difficult to ensure that all imported medicines are indeed licensed. According to a WHO estimate, 74 % of the regulatory authorities of the 194 member states were classified as not "stable and well-functioning" in 2019 (WHO 2021a). Poor ethical practice due to corruption is a further problem. Once substandard or falsified medicines have entered the country, weak pharmacovigilance and post-marketing surveillance systems allow them to remain undetected and to cause harm to patients. Weak NMRAs, poor health supply chain systems and high prices of medicines from legal sources also foster flourishing black markets in LMICs: unavailability of essential medicines in the hospitals and health centers, as well as lack of appropriate health insurance, drive patients to black markets that are often well stocked and less expensive. On the black markets, however, substandard and falsified medicines are highly prevalent, and correct storage conditions are often not maintained, increasing the likelihood of product degradation (WHO 2017a).

High-income countries, for example in Europe, are also affected by the problem of SF medicines, especially due to the popularity of e-commerce and online pharmacies. Medicines from unauthorised sources can easily enter this market, as the access barriers are low while the business model appears highly profitable (WHO 2017a; Dellasega and Vorrath 2020). The magnitude of this rapidly growing market for SF medicines is adumbrated by the amounts of seizures and arrests of INTERPOL's latest Operation Pangea (INTERPOL 2021b).

In Europe, the (legal) practice of parallel trading also represents a possible entry point for substandard or falsified medicines. Parallel trading takes advantage of price differences between markets in different countries, as well as differences in health care financing regimes and fluctuations of exchange rates: goods are bought in lower-priced markets, to be repackaged for resale in higher-priced markets. Often several distributors and traders are involved, increasing the opportunities for the entry of falsified products.

*Examples of substandard and falsified medicines detected in high-income and in low- and middle-income countries*

The following examples may illustrate how the complex global supply chains facilitate the entry of SF medicines and how the Global North is connected with the Global South in regard to this problem. They also stress the importance of reporting and communication between stakeholders in different world regions, e.g. via WHO, in order to detect SF medicines.

**Falsified Avastin® in the United States:** In 2012, falsified vials labeled as Avastin® (bevacizumab), a cancer drug costing about US$2,400 per vial, reached patients in the United States. They contained no API. At least 19 medical doctors had bought vials of this preparation from a distributor in Montana (US) under its Turkish brand name Altuzan®, at a price about US$500 lower than the US market price at that time. The US distributor had bought the medicine via the internet-based pharmacy of a wholesaler in the United Kingdom. This UK-based wholesaler had purchased the vials from a Danish company, which in turn had received them from a Swiss company who in turn had bought them from an Egyptian businessman. The Egyptian businessman had obtained the medicine from a Syrian dealer, apparently believing that it was the genuine product manufactured in Turkey (Keteyian 2012; WHO 2017a). This example shows the complexity of international supply chains, which can make it very difficult to trace the origin of a given medicine.

**Falsified Herceptin® in Germany:** In 2014, falsified Herceptin® (trastuzumab), an antibody against different types of cancer, was found in Germany (Streit 2017). The medicine showed different batch numbers on the primary and the secondary packaging, and some vials contained a liquid instead of a lyophilised powder. At least one vial contained the antibiotic ceftriaxone instead of trastuzumab (Streit 2017; Roche Pharma AG 2014). Apparently, the medicine had been stolen in Italy and had entered the legal supply chain via parallel trading. It was found not only in Germany but also in Finland, Austria, Sweden and the UK. The German parallel trader had obtained the medicine from two British distributors, who were supplied by an Italian distributor, who, however, had never been supplied by the manufacturing company, Roche. It turned out that further high-value medicines had also been stolen from hospitals in Italy, or from trucks delivering to these hospitals, and had then entered the legal supply chain in Germany and other European countries. It was suspected that Italian and East European mafia groups might be behind the thefts (Dugato, Riccardi and Polizzotti 2014).

**Levomethorphan-containing cough syrups in Pakistan and Paraguay:** In early 2012, 60 adults in two cities in Pakistan died (WHO 2013a, 2013b). As drug addicts, they had consumed large quantities of cough syrups. Investigations revealed that the two local manufacturers of these syrups had recently changed the source of the API, dextromethorphan, to a cheaper supplier from India. It was discovered that this material also contained the enantiomer of dextromethorphan, levomethorphan, which is a potent opioid analgesic, five times stronger than morphine (Wainer 1996). Few laboratories have reference samples of this strictly controlled drug substance, and it is difficult to distinguish it in chemical analysis from the cough suppressant dextromethorphan. In a separate event in September 2013, 44 children were admitted to a hospital in Paraguay after being treated for influenza-like symptoms with a cough syrup (WHO 2013b). An alert to the national authorities and to WHO allowed the similarity to the case in Pakistan to be recognised, and Paraguayan investigators found import records for the same dextromethorphan batch from India which had been supplied to the two manufacturers in Pakistan. The affected batches had been exported to several countries in Europe, North Africa, the Middle East and Latin America. In both Colombia and Peru, manufacturers had already used the contaminated batches to produce cough syrup – fortunately, the products were recalled and never reached the patients in these countries (WHO 2017a).

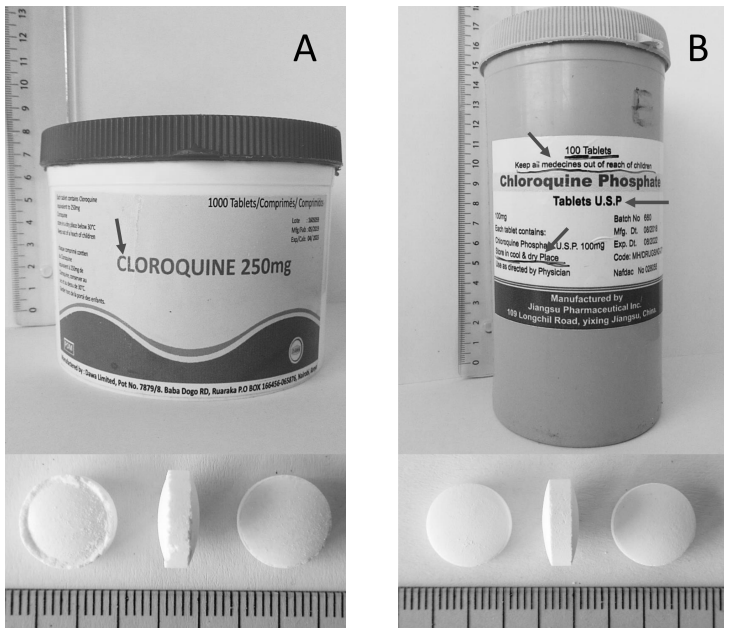
**Substandard misoprostol tablets in Malawi:** In 2017, extremely substandard misoprostol tablets were found in the legal supply chain in Malawi (Hagen, Khuluza and Heide 2020). The tablets contained only 13 % of the declared content of misoprostol. Misoprostol is very instable, especially in humid conditions. Appropriate primary packaging such as double-sided aluminium blisters is therefore important to protect the misoprostol tablets from degradation (Hall and Tagontong 2016). In the substandard product, however, the tablets were only packed in plastic-aluminium blisters, which is insufficient to protect misoprostol from humidity. Chemical analysis revealed high amounts of the typical degradation products of misoprostol. Malawian authorities and WHO were informed about these findings, which led to a nationwide recall of the substandard product (Hagen, Khuluza and Heide 2020). The product had been distributed by a British distributor. Notably, this distributor was located at the same address and was apparently managed by the same family as a distributor company who had been reported to distribute substandard propofol, an anaesthetic, to the government of Zambia (Mumphansha et al. 2017). Through WHO, the British regulatory agency (MHRA) was informed. It initiated an investigation, and both distributor companies went

into voluntary liquidation shortly thereafter (Hagen, Khuluza and Heide 2020). There is no information about any subsequent legal proceedings against the responsible persons. However, according to the UK company register Companies House, the same owner family still appears to run several pharmaceutical wholesale companies (Companies House 2021).

### *Substandard and falsified medicines and the COVID-19 pandemic*

As a consequence of the COVID-19 pandemic, the supply chains for both raw materials and finished pharmaceutical products were frequently disrupted. For example, since the beginning of the COVID-19 pandemic, there was a global-level shortage of over 20 medicines, including four controlled substances according to WHO. In a joint statement, the International Narcotics Control Board (INCB), UNODC and WHO (2021) therefore called for facilitated access to (controlled) medicines in emergencies, such as climate-related disasters and the current COVID-19 pandemic. Supply bottlenecks in legal markets, the increasing demand for certain medical goods and suspended in-person inspections of pharmaceutical facilities by regulatory bodies due to COVID-19 are factors that facilitate the emergence of substandard and falsified medicines (Newton et al. 2020; Dellasega and Vorrath 2020). The COVID-19 pandemic provides examples of how quickly criminal manufacturers and traffickers of falsified medicines react to an increased demand for certain medicines. From February 2020, reports about a possible effectiveness of chloroquine and hydroxychloroquine against COVID-19 received massive media attention worldwide, and the demand for these two medicines skyrocketed (Newton et al. 2020). Only a few weeks later, falsified chloroquine tablets were detected in pharmacies and at informal vendors in Cameroon and the Democratic Republic of Congo (Fig. 3) (Gnegel et al. 2020; WHO 2020c). They contained little or no chloroquine. However, some of them contained small amounts of paracetamol and/or of the bitter-tasting antibiotic metronidazole, possibly to mimic the bitter taste of chloroquine. The labelling of the falsified samples contained mistakes and spelling errors – an indication that they were produced by criminals and not by established manufacturers. The dosage of metronidazole was subtherapeutic, which may lead to the emergence of antimicrobial resistance. These findings were amongst 14 reports of confirmed falsified chloroquine products from five different countries in Africa and Europe (WHO 2020c).

*Figure 3: Falsified chloroquine tablets collected early in the COVID-19 pandemic in Cameroon and the Democratic Republic of Congo. The labels contain spelling errors (marked here with arrows), and the tablets of sample (A) are very poorly manufactured (Photo: Gesa Gnegel, Tübingen University, 2020).*




In March 2020, WHO published an alert about "Falsified medical products, including in vitro diagnostics, that claim to prevent, detect, treat or cure COVID-19" (WHO 2020b). In December 2020, INTERPOL issued an Orange Notice to warn about organised crime networks targeting COVID-19 vaccines (INTERPOL 2020b). Just a few weeks later, around 2,400 doses of fake COVID-19 vaccines were found in South Africa, as well as a large number of fake masks, leading to four arrests (INTERPOL 2021a). Also, in China, more than 3,000 doses of fake COVID-19 vaccines were seized, and 80 suspects were arrested (INTERPOL 2021a).

With the annual Operation Pangea, INTERPOL targets the illegal sale of medicines. In the 2020 Operation Pangea XIII, INTERPOL reported a 100 per cent increase in seizures of unauthorised chloroquine compared to the previous year (INTERPOL 2020a). The 2021 Operation Pangea XIV led to 277 arrests and seizures of potentially dangerous pharmaceuticals worth US$23 million. Additionally, 113,020 web links of fake online pharmacies

and marketplaces were closed down or removed – the highest number so far since the first Operation Pangea in 2008. More than half of all medical devices seized were fake and unauthorised COVID-19 testing kits (INTERPOL 2021b).

The Medicine Quality Research Group at Oxford University, UK, monitors all reports in the public domain on substandard and falsified medical products related to COVID-19. Between 12 March 2020 and 31 May 2021, they found 123 reports of diverted or SF COVID-19 vaccines from 35 countries and/or online in the lay press (Van Assche, Caillet and Newton 2021b).

### *Recommendations for tackling the trade in substandard and falsified medicines*

As summarised in the report on the WHO Global Surveillance and Monitoring System, the key elements in addressing the problem of substandard and falsified medicines are prevention, detection and response (WHO 2017a). To prevent SF medicines from entering the supply chains, it is crucial to improve availability, accessibility and affordability of medicines of good quality through the legal supply chain. If this is achieved, the demand for medicines from outside the legal supply chain will diminish, and the trade with SF medicines will become less attractive. Quality assurance in medicine procurement must be strengthened, following e.g. the "WHO quality assurance policy for the procurement of essential medicines and other health products" (WHO 2021e). The WHO Prequalification of Medicines Programme is a further very important contribution to this goal (WHO 2021c).

Track-and-trace systems such as the securPharm system, which commenced operation in Germany in 2019 in accordance with the EU Directive for the prevention of the entry into the legal supply chain of falsified medicinal products (Bergen and Hoferichter 2017), are very effective but costly. (Mobile) authentication applications are another, more affordable option, such as the Mobile Authentication Service (MAS), used by the National Agency for Food and Drug Administration and Control of Nigeria (NAFDAC) since 2010 (Oyetunde et al. 2019). WHO recently published a policy paper on traceability of medical products (WHO 2021b).

Field detection devices for rapid screening like the Minilab® of the Global Pharma Health Fund (GPHF 2021) or portable devices for infrared or Raman spectroscopy (Vickers et al. 2018) can help to detect substandard and falsified medicines which have entered into the supply chains and allow a more effective use of the costly resources of fully equipped medicine

quality control laboratories. Recently, a chapter was added to the United States Pharmacopeia (USP) entitled "Evaluation of screening technologies for assessing medicine quality", acknowledging the benefits of such devices (USP 2020). The aim is to establish the capabilities and limitations of these devices.

To be able to respond appropriately to the problem of SF medicines, it is important to assess the scope of this problem in different geographical regions, in different parts of the health supply chain and for different types of medicines via systematic research, in accordance with current standards such as the WHO "Guidelines on the conduct of surveys of the quality of medicines" (WHO 2016) and the MEDQUARG guidelines (Newton et al. 2009).

A key aspect for mounting a response to SF medicines is strengthening the NMRAs – only with the right equipment and well-trained staff will these authorities be able to tackle the tasks required to assure the quality of medical products. Control mechanisms between and within authorities are necessary to fight corruption at all levels of the supply chain. In addition, stronger networking between health actors, regulatory authorities, law enforcement and customs leads to improvements in pharmaceutical surveillance (Vorrath and Voss 2019).

Communication between all stakeholders is important, as well as publicly sharing the data on SF medicines: if the precise problems are not known, precious resources are wasted in the response. The general public can be involved with awareness-raising campaigns, and civil society organisations may be important contributors in this regard. There are also initiatives to improve reporting and interventions by frontline healthcare professionals, specifically in regions with a high burden of SF medicines. For example, together with WHO the International Pharmaceutical Federation developed a compulsory education component on SF medicines that was introduced in five universities in Sub-Saharan Africa as part of a pilot project (FIP 2021). In this curriculum, pharmacy students learn how to avoid, detect and report SF medicines. Further, the United States Agency for International Development (USAID) and the USP collaborate with Nigerian universities in the course of their Promoting the Quality of Medicines (PQM) programme to strengthen the teaching on quality control in the curriculum of pharmacy students (PQM 2018).

A shared legal understanding between countries is necessary to respond appropriately to illicit trade of SF medicines. As long as penalties for the manufacture or trade of SF medicines are low, the benefits outweigh the risks for the criminals, and SF medicines will continue to be a global threat. UNODC (2019) has published a guide to good legislative practices

to combat falsified medical product-related crime, and a model law on medicine crime has been suggested by Attaran (2015). Similarly, the MEDICRIME Convention of the Council of Europe provides countries with a model legal framework dealing with falsified medical products. The intention of this guide is to support states in enacting or strengthening domestic legislation regarding falsified product-related crime (Alarcón-Jiménez 2015). Specific laws for pharmaceutical crime, cross-border information sharing and cooperation in law enforcement as well as control mechanisms between and within relevant agencies are also needed to counter crime related to SF medicines (Dellasega and Vorrath 2020; Vorrath and Voss 2019). Effective joint law enforcement such as INTERPOL and custom controls have already led to some successes in the fight against SF medicines, for example with Operation Pangea, and they will also remain an important intervention to limit the extent of the trade with SF medicines.

SF medicines have a global impact – both in the Global North and in the Global South. The threat that is emerging from SF medicines for individuals, health systems, economies and states can therefore only be successfully addressed with the united, global participation of all parties involved. The authors of a Lancet comment rightly call for global interventions to ensure access to affordable, good quality medical products worldwide and stress that the world's population will depend on it as "[a]ll our fates are bound together" (Newton et al. 2020: e754).

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