Oncology drugs clearly have become a target for pharmaceutical crime. In 2016, falsified oncology drugs ranked fifth in the most commonly falsified drug category among the reports received by the Pharmaceutical Security Institute. Although the prevalence of illicit oncology drugs in the legal supply chains appears to be small, these drugs are difficult to detect, particularly in clinical practice. Forthcoming countermeasures to detect illicit drugs in high-income countries include compulsory antitampering devices and product verification technology for a risk-based selection of medicines. Health-care professionals must implement these new procedures into their workflow and remain vigilant about those medicines that are not selected. Although countermeasures should firmly tighten supply chain security, there are concerns about how quickly pharmaceutical crime will adapt to these protections. Because patients and health-care professionals have shown a lenient attitude towards purchasing medicines from unreliable sources, measures against the highly accessible illegal medicine supply chain remain necessary. To improve detectability in clinical practice, reporting of ineffectiveness and unusual drug effects as adverse events or adverse drug reactions is essential.

Introduction
The plainest description of a falsified medicine is a medicine that is not what it appears to be by malicious intent. This means that anyone at the manufacturing, wholesale, or dispensing level has falsified either the drug, the labels, the packages, distribution, or any other connected documentation concerning the drug (figure). Falsification might also involve active ingredients or excipients supplied to the pharmaceutical manufacturer and the diversion of the genuine finished product to sources other than the intended recipient. Diversion of pharmaceuticals can be understood as a series of criminal practices in which medicines intended for a particular market are diverted to be sold in another market. Examples of diversion include the laundering of stolen medicines with false documentation and the export of medicines obtained with false prescriptions. Falsified medicines should not be confused with substandard medicines, a term that is used to describe genuine medicines obtained with false prescriptions. Additionally, the absence of a global consensus on the appropriate terminology in this domain has made it difficult to select suitable search terms. For instance, the word counterfeit is interpreted differently in various regions of the world, and these interpretations have been prone to change as the world has gradually been moving towards a consensus in terminology. We searched for literature on falsified medicines, particularly falsified oncology medicines, using Embase, and the Google search engine was used to search for grey literature, government reports, and websites for additional information. Additionally, public documents on cases and incidents known to the authors were brought in when considered appropriate. Substandard medicines were not considered within the scope of this Series paper as resolving unintentional quality defects requires different regulatory actions.

History
Many countries around the world are affected by falsified medicines. Low-income and middle-income countries have typically faced substandard and falsified medicines penetrating their markets. Although literature reports mostly focus on falsified antimalarials, the range of falsified medicines spans many therapeutic areas. In high-income countries, substandard or falsified medicines in the legal supply chain were rarely reported in the 1990s. However, an upsurge emerged after the introduction of the erectile dysfunction drug sildenafil on the US legal market in 1997. Drug regulatory authorities in North America, Europe, and Asia soon noticed an illegal trade in erectile dysfunction drugs on the nascent internet. The rise in ecommerce platforms and increased access to informal economies and grey markets contributed to the establishment of an illegal supply chain. Criminals became attracted to pharmaceutical crime for its financial market potential, the small risk of being apprehended, and modest
For more on the Permanent Forum on International Pharmaceutical Crime see http://www.pfipc.org/
For more on the International Laboratory Forum on Counterfeit Medicines see http://www.pfipc.org/
international-laboratory-forum-on-counterfeit-medicines

Figure: Product flow in the legal supply chain and the possible connections with the illegal supply chain

Pharmaceutical crime might: (A) falsify authentic medicines through theft and diversion; (B) insert substandard and falsified raw materials at the manufacturing level; (C) insert substandard and falsified medicines at the level of distribution and at the level of health-care professionals; (D) collect authentic product parts for falsification purposes; and (E) sell substandard and falsified, unauthorised, or unlicensed medicines to patients directly.

Penalties. By 1998, several national drug regulatory authorities established the Permanent Forum on International Pharmaceutical Crime and the International Laboratory Forum on Counterfeit Medicines. These international expert groups of enforcement officers, pharmaceutical scientists, and forensic scientists have since advised on the protection of the legal supply chain and how to combat the illegal supply chain. Since then, many other organisations have become involved, ranging from members of the pharmaceutical industry to consumer protection organisations. Having started with poor imitation products, pharmaceutical crime gradually progressed to selling medicines that appear genuine and trustworthy. Evidence suggests that criminals became aware of standard quality testing protocols and have used that knowledge to avoid or to delay detection. If the falsified trastuzumab had reached the illegal supply chain in several EU countries before it had been retrieved from hospital waste, with an unknown criminal group produced completely fake versions of the falsified trastuzumab by refilling used injection vials, which had been discovered in Europe in 2014. The stolen batches were stored and distributed in facilities that did not have temperature control, which risked the degradation of the active ingredients in the product. The falsified trastuzumab was discovered by a German distributor and was recalled from the legal supply chain in the EU. The stolen batches were stored and distributed in facilities that did not have temperature control, which risked the degradation of the active ingredients in the product. The falsified trastuzumab was discovered by a German distributor and was recalled from the legal supply chain in the EU. Falsification is usually first detected in the distribution part of the legal supply chain, regardless of whether patients have already been treated with these products. Falsified products have also been circulated by operators in the legal supply chain. In one case, batches of the chemotherapeutic thiotepa had expired, and degraded lots of the alkylating agent were relabelled with a new batch number and expiry date.

The falsification was done by a Swiss manufacturer and wholesaler and the products were released on the French market between 2007 and 2011. After being discovered in 2011, these falsified products were recalled in the same year. The incidents with trastuzumab in Europe, in 2014, bear the hallmarks of organised pharmaceutical crime. In this case, a criminal network provided stolen batches of authentic trastuzumab with fake documentation and reintroduced them into the legal supply chain in the EU. The stolen batches were stored and distributed in facilities that did not have temperature control, which risked the degradation of the active ingredients in the compound. The falsified trastuzumab was discovered by a German distributor and was recalled from the legal supply chain in several EU countries before it had reached patients. At roughly the same time, another criminal group produced completely fake versions of trastuzumab by refilling used injection vials, which had been retrieved from hospital waste, with an unknown solution.

If the falsified trastuzumab had reached patients, it might have seriously affected or delayed their treatment course and outcomes, depending on how many effective treatments would have been missed. Furthermore, the unknown solutions used to prepare the counterfeit products could have been clinically dangerous to patients. On top of that, sterility might have been compromised during the falsification process, putting patients with cancer, who were already severely immunocompromised, at risk of infection and further complications of disease.

Theft of expensive oncology drugs and product tampering are recognised as growing concerns in the medical supply chain because these medicines are likely to be diverted to another supply chain or clinic, resulting in the administration of falsified drugs to patients. In terms of volume, the main threat nowadays comes from medicines that are—wittingly or unwittingly—purchased from the illegal supply chain by patients or health-care professionals alike. In a 2014 study, the UK Royal United Services Institute noticed a lenient attitude among the British public towards purchasing medicines outside of the legal system. 10 years of annual Operation Pangea seizures have confirmed that the illegal supply
chain flourishes around the globe. In those 10 years, the number of participating countries increased about ten times, from ten to slightly above 100. During that period, the number of seized shipments increased more than 20 times and, since 2013, the value of the products seized in 1 week ranges between US$32 million and US$1 million. These seizures are dominated by imports of unlicensed and unauthorised medicines ranging from lifestyle medicines to life-saving drugs. However, there are no methods available to assess the actual use of medicines obtained from the illegal supply chain, with the exception of a specific method to measure the use of illegally supplied sildenafil, which uses waste water analysis. This method is not generally applicable to most falsified medicines because waste water analysis requires the illegal supply chain to have a considerable market share of the total supply of the drug.

Although falsified oncology drugs have been reported in Operation Pangea, the literature has shown no examples of patients, or their kin, having purchased cancer treatment from unreliable sources. For health-care professionals, however, the opposite has been shown. According to the literature, the US FDA recorded 145 medical practices in the USA between 2007 and 2013 that might have purchased falsified oncology drugs. In some cases, health-care professionals ignored warning letters issued by the regulator about the use of falsified medicines and continued treating patients with counterfeit bevacizumab. Although harm is imminent when falsified medicines are used, case reports of harm caused by falsified oncology drugs are scarce, and the literature has shown that this is true for falsified medicines in general. In countries that allow direct marketing to health-care institutes, such as the USA, staff are at risk of purchasing drugs from the illegal supply chain, as was the case with the use of falsified bevacizumab in the USA in 2012–13.

### Harm

Pharmaceutical analysis of seized falsified medicines has shown that these medicines can contain no active ingredients, the wrong dose, the wrong active ingredient, and hazardous impurities. Consequently, a patient’s medical condition can be jeopardised by an absence of effectiveness or intoxications and unexpected interactions when they are treated with falsified medication. According to the literature, there is a considerable under-reporting of harm. Such underreporting is illustrated by a case in the US legal supply chain in which up to 110000 patients received medication from erythropoietin 2000 U vials that had been falsely relabelled as erythropoietin 40 000 U. Despite the vials containing just 5% of the labelled concentration, an absence of effectiveness was only reported in two patients—a patient who had received a transplant and a patient with breast cancer. Similarly, in the UK, at least 70 000 packs of bicalutamide, a prostate cancer drug, the anticoagulant clopidogrel, and the antidepressant olanzapine entered the legal supply chain. The case unfolded after falsified clopidogrel was noticed during a UK clinical study and the FDA identified the distributor. The falsified products contained 50–80% of the declared concentrations of the active ingredient, resulting in patients receiving an inadequate dose of treatment. Because lot numbers, at the time, were not tracked throughout the legal supply chain, some 30 000 packs were consumed by patients who could not be traced. Despite this number of consumed falsified medicines in the UK, no absence of effectiveness has been reported through the official reporting system.

According to International Council for Harmonisation guidelines, absence of effectiveness is an adverse event. Despite being a specific signal for the presence of a falsified medicine, this event is not necessarily suspect in clinical practice. Yet, reports of an absence of effectiveness to pharmacovigilance systems can play a pivotal role in the detection of falsified medicines. In the USA, a falsified insulin analogue was identified in the legal supply chain after an unusual string of adverse event reports describing an absence of effectiveness. Subsequent investigations revealed that the drugs in question were authentic products from a stolen consignment that had degraded because of improper storage.

Other specific signals for falsified medicines are unusual, acute, and serious adverse events or adverse drug reactions. One incident of falsified bevacizumab in the US legal supply chain was detected after a nurse reported an unusual reaction to the product. However, more frequently, a series of similar adverse events or adverse drug reactions need to be reported for a falsification incident to be detected. Falsified heparin was detected in the legal supply chains worldwide after a surge in submissions of similar serious adverse event reports in the USA. It transpired that a legitimate pharmaceutical industry had been supplied with heparin that had been adulterated with an unknown heparin analogue. The adulteration was done in such a way that the active ingredient met its necessary specifications without the adulterant being detected in the required quality tests. This cunning scheme contributed to the deaths of many patients (some estimates point to more than 200 deaths worldwide) and, without adequate adverse event reporting, the situation could have become more widespread. In another case example in southeast Asia, in 2008, sildenafil became mixed with the antidiabetic drug glibenclamide. The mixing occurred at some point in the active ingredient trade, which led to the identification of the combination of these two drugs in many different unapproved brands of erectile dysfunction medicines. The mix-up of active ingredients was first discovered at the hospital level because of outbreaks of severe hypoglycaemia in Hong Kong and
Singapore. The fact that hypoglycaemia is not a known adverse effect of erectile dysfunction drugs, along with patients being reluctant to admit to using such drugs, delayed the discovery of the cause of the outbreak.

The literature describes several successful retrospective studies that identified harm caused by falsified medicines in the databases of poison centres and pharmacovigilance units. A prospective study using a decision tool for physicians was mounted by the European Directorate for the Quality of Medicines and Health Care and its Expert Committee for Counterfeit Medicines. The objective of the study was to improve the recognition of harm on the basis of the expected clinical symptoms and signs of falsified medicines from the KnowX database of the European Directorate. This database aggregates the cases of falsified medicines collected by official medicines control laboratories, health authorities, police, and customs. The approach was successful, and several cases possibly involving falsified medicines have been identified by use of the decision tool. Further development should make this method practical in a clinical setting in which time is a constraining issue.

Regulatory responses and countermeasures

After a steady increase of incidents with falsified medicines since the turn of the century, organisations such as WHO, the Council of Europe, the EU, and the FDA became actively involved in the fight against these crimes and set out to protect patients and secure victims’ rights. Internationally, efforts were slowed down by lengthy discussions about finding an accepted terminology for substances that were colloquially referred to as counterfeit or illegal medical products. The root problems were that the term counterfeit is considered by many countries to be linked to intellectual property rights, and the term illegal was deemed too vague because something illegal in one country might be legal in another. In 2009, WHO agreed on temporarily using the term substandard, spurious, falsely-labelled, falsified, and counterfeit medical product. Afterwards, this term was changed to substandard and falsified medical product by the member state mechanism of WHO and was adopted by the World Health Assembly in May, 2017.

The Council of Europe adopted the Medicrime Convention in 2010, with the intention of avoiding long discussions on terminology, and decided on the use of the term counterfeit, but emphasised that this term had no connection to intellectual property rights. The convention defines counterfeit as "a deliberately false representation of its identity and/or source". A slightly modified definition was later adopted by the EU in 2013, when the Falsified Medicines Directive was issued, which then made official the commonly used term falsified. The member state mechanism of WHO has also adopted the EU definition but without the word history, to separate unlicensed from unauthorised medical products. Unauthorised products also pose a health threat, but require a different regulatory response than unlicensed medicines.

The Medicrime Convention is the only international legal framework to help fight against falsified medical products and similar crimes, applying a three-fold focus: providing the basis for the criminalisation of particular acts; protecting the rights of victims of the offences established under the convention; and promoting national and international cooperation. Only intentional breaches of quality norms, good practices, and standards in the manufacture and distribution of medical products are subject to the convention. As the falsification of medical products and similar crimes constitutes a global threat, the convention is open to member and non-member states of the Council of Europe. As of November, 2017, the convention was signed by 27 countries and subsequently ratified by 11. After the tenth ratification in August, 2017, the convention’s monitoring body—the Committee of the Parties—should be set up within the following 12 months.

The European Commission issued the Falsified Medicines Directive in 2011, and it has been legally applied since January, 2013. The directive introduced tougher rules to improve the protection of public health, with harmonised European measures to ensure that medicines are safe and that the trade in medicines is rigorously controlled. To this end, these new measures include: obligatory safety features on the outer packaging of medicines; a common, EU-wide logo to identify legal online pharmacies; tougher rules on the controls and inspections of producers of active pharmaceutical ingredients; the definition of the activities of all actors, such as brokers, which can play a role in the distribution channel for medicinal products; and strengthened record-keeping requirements for wholesale distributors. The Falsified Medicines Directive differs from the Medicrime Convention in that it provides measures to secure and regulate the legal supply chain, whereas the Medicrime Convention is a criminal law convention in which countries need to adjust their penal code to allow appropriate means of investigation, prosecution, and sentencing in response to crimes related to the illegal supply of falsified medicines.

Under the Falsified Medicines Directive, the manufacturers must place a unique identifier on the packaging of a medicinal product in the form of a two-dimensional barcode containing data elements defined in the delegated regulation 2016/161. The unique identifier codes and anti-tampering devices are necessary for medicines with a high risk of being falsified (eg, high-priced medicines), not only because criminals are technically able to rapidly copy overt security features, but also to prevent the reintroduction of stolen lots and those that might have been tampered with. Therefore, these two measures apply to a selection of medicines that is prone to change with the focus of pharmaceutical...
crime. By 2019, the Falsified Medicines Directive will require a systematic serialisation in production and a verification step at the point of supply to the patient throughout the EU and the European Economic Area. Health-care professionals will have to devise and implement new procedures to convert these measures into practice, including follow-up steps for when suspicious products are detected. A study in which a verification system such as the one envisioned by the Falsified Medicines Directive was used in a UK hospital showed that the system performed below expectations because of low adherence.

In 2013, the USA launched the Drug Supply Chain Security Act to facilitate the tracing of a risk-based selection of prescription medicines through the legal supply chain. The act requires the verification of a medicinal product at each change of ownership in the supply chain, but not at the point of dispensing to the patient. In India, China, and African countries, new legislation has been drafted to strengthen the legal protection of medicinal products. Several initiatives, such as the use of handheld screening devices, have been launched that aim to enable health-care professionals and patients to verify the authenticity of a medicinal product. Nevertheless, these regions are also faced with falsified medicines available in the illegal supply chain.

Discussion

The economic forces of supply and demand are no strangers to the field of medicine. What makes this field stand out from other economic areas is the vulnerability of the patient and the inextinguishable demand for treatment. As with drug trafficking, the supply of falsified medicines is about meeting the demand unnoticed. The literature shows that falsified medicines that do not produce strong clinical effects can be broadly used by patients without raising alarm. Hence, pharmaceutical crime can be expected to try to stay unnoticed by pharmacovigilance systems. Oncology drugs such as rituximab, bevacizumab, and trastuzumab are interesting targets for illicit handling because of the high demand for life-saving medicines, the potential profit per unit, the fact that product quality is not easily checked because these drugs are colourless fluids, and because an absence of effectiveness does not automatically arouse suspicion.

Quantifying the harm caused by falsified medicines has been one of the principal challenges of the past two decades. Overall, there is still insufficient information available worldwide to assess the threat that these products pose to patients and to society. National drug regulatory authorities might contribute to the awareness of the issue by sharing more cases involving falsified medicines. The website of the German Federal Institute for Drugs and Medical Devices is well maintained in that respect. Reservations about transparency are understandable because such information could trigger unnecessary panic. However, if cases do not make it to the public domain they might as well never have happened. If health risks and harm are not sufficiently acknowledged, the problem is easily overlooked.

The countermeasures that should make pharmaceutical crime less attractive are in full swing. The EU Falsified Medicines Directive, the US Drug Supply Chain Security Act, and other initiatives will hopefully provide for more secure supply chain, while the Medicrime Convention allows for the prosecution and appropriate punishment of these crimes. These different measures complement each other and are necessary for successful protection of the public against falsified medicines. Yet, there are a few concerns. First, pharmaceutical crime has shown that it is very adaptive and quick to circumvent new security measures, and the demand for medicines is growing. Whether the planned countermeasures are effective, or how this effectiveness will be measured remains to be seen. Even if pharmaceutical crime focused on less regulated regions of the world, falsified medicines would still be accessible on the world market. Second, updating supply chain security might put additional strain on budgets and working procedures in health care. This additional strain might inadvertently keep the legal supply chain attractive to pharmaceutical crime. Third, the existence of a highly accessible global illegal supply chain, and the lenient attitude of the public towards it, undermines the efforts to fight pharmaceutical crime. A major issue is that the illegal supply chain seems to be aiming to have returning customers by supplying effective but unlicensed and unauthorised medicines. Even if the product quality would be acceptable, there are risks associated with the user because the medicine might not be appropriate for the user’s needs.

Tightening supply chain security is turning the role of the health-care professional into somewhat of a gatekeeper at the end of that chain. Verification of the authenticity of medicines that are equipped with a unique identifier might be quick, but for other medicines, it will remain tedious and difficult because falsifications might look convincing. Matters are further complicated by frequent changes in authentic packaging and brands that are reimbursed. Recognising a falsified medicine by its clinical effects is also not straightforward. Although one single report might suffice, identifying cases of harm mostly relies on a critical mass of seemingly indistinct signals being reported. Pharmacovigilance holds an important position in filtering out adverse event reports that could be due to substandard or falsified medicines. At the end of the protected legal supply chain, health-care professionals should be aware that they too are a target for pharmaceutical crime. They should also be aware that their patients might have purchased medicines from the illegal supply chain and should ask their patients whether they are consuming medicines from other sources besides the ones that have been officially prescribed.
Because internet purchases of medicines by patients are expected to increase even further, it is wise to empower patients in making the right choice.\textsuperscript{31-33} Therefore, the EU common logo for bona fide internet pharmacies is a step in the right direction. The next step is staying ahead of online pharmaceutical crime. In that respect, it might be necessary to reduce legislative differences between countries by achieving international consensus, because patients are no longer bound to purchasing illegal medicines within their national borders. Additionally, on the legal market, patients will be drawn to internet pharmacies from countries with the least restrictions and lowest prices. Increased coherence in the legal supply chains will more clearly draw the lines between right and wrong. Technology that enables health-care professionals and patients to verify the authenticity of a medicinal product is a valuable development.\textsuperscript{24,37} Obviously, such verification technology must be well protected from the influence of pharmaceutical crime. In low-income countries with restricted access to medicinal products, the verification of product quality might be more appropriate and crucial than the verification of market authorisation.

The judicial area has made important progress on falsified medicines over the past 20 years.\textsuperscript{7,44,52,117} However, even within the EU, the legal situation of pharmaceutical crime still varies greatly from one member state to another.\textsuperscript{89} In most countries of the world, pharmaceutical crime is a violation of a medicines act rather than a crime, and this distinction has consequences for enforcement priorities, resources, sanctioning, and victims’ rights. Even in the European case regarding trastuzumab,\textsuperscript{90} more than 80 people could only be charged for theft and money laundering because there was no specific sanction for the intentional distribution of falsified medicines. A similar outcome was faced by health-care professionals and brokers who were prosecuted for their part in the case of counterfeit bevacizumab that was detected in the US drug supply chain.\textsuperscript{33} In this case, multiple defendants were prosecuted for charges associated with regulatory violations, including distribution of adulterated products, fraud, trafficking, and trade of fake products, and criminal charges such as wire fraud, with no prosecutions associated with patient injury or safety. It is a general issue with pharmaceutical crime that sanctioning and victims’ rights depend heavily on victims being identified and being able to show the incurred harm. In the previously mentioned case of the sildenafil–glibenclamide mix-up, this issue might not have been overly complicated, because there were noticeable adverse events detected.\textsuperscript{84,85} But what harm does a patient with cancer sustain when receiving an ineffective treatment cycle, and can that harm be proven in a court of justice? The Medicrime Convention addresses this judicial issue by stating that a harm be proven in a court of justice? Moreover, if the incurred harm would result in the death of the individual, this could be considered an aggravating circumstance. The convention also provides for “assisting victims in their physical, psychological, and social recovery”. However, ultimately, the key issue that remains is the identification of falsified medical products and its victims.

**Conclusion**

Falsified oncology drugs have regularly been detected in countries around the world. The scale of infiltration into the legal supply chain appears to be small, but low detectability is an issue, particularly in a clinical setting. The introduction of antitampering devices and unique identifier codes for medicines with a high risk of being falsified will assist in the recognition of falsifications before they reach patients. However, at the patient level, chances that falsified oncology drugs are recognised are still slim, unless they generate a sufficient number of adverse events or adverse drug reaction reports. Health-care professionals can make a difference by reporting unusual effects or an absence of effectiveness, even when these events are not suspicious at face value. A single report to pharmacovigilance authorities might be enough to expose falsified medicines.

Falsified medicines reach health-care professionals and patients through both the legal and the illegal supply chains. Without improved data on the scale and the severity of the problem, it is hard to decide what countermeasures are needed in proportion to the problem. Updating the legal supply chain with improved product traceability and verification technology is a step forward in the right direction. Further updates are probably necessary because pharmaceutical crime can be expected to adapt. Additionally, the fortification of the legal system must be matched by adequate measures against the illegal supply chain. Purchasing from the illegal supply chain is not just about risking one’s personal health, but also about undermining a health-care system.

The strong mutual trust that justly exists within the legal supply chain is both its strongpoint and its weakness. It is a strongpoint because this trust allows for a smooth distribution of medical products, but is also a weakness because it might hinder the vigilance that is required at all stages. Neither physicians nor patients should be overly burdened, or preoccupied, with verifying the authenticity of medicines. To clinical practice, fighting falsified medicines means reporting adverse events, adverse drug reactions, and suspect products through the established channels. Patients should be asked about where they purchased any additional medications from, and health-care professionals should be aware that both they and their patients are a target for pharmaceutical crime.

**Contributors**

All authors contributed equally to the design of the manuscript. BJV drafted the first version of the manuscript. AEO created the artwork. All authors contributed equally to finalising the manuscript.
Declaration of interests
We declare no competing interests.

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