

Securing the Global Pharmaceutical
Supply Chain against the Threat of
Counterfeit Drugs.

JUNE 2014



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Securing the Global Pharmaceutical Supply Chain against the Threat of Counterfeit Drugs

In 2012, counterfeit versions of the cancer drug Avastin were found in 19 American treatment centers. The impostor drug lacked the active ingredient, rendering it virtually useless for treatment purposes. The same year, counterfeits of Viagra and Cialis smuggled into the U.K. were found to contain undeclared active ingredients that posed potentially serious health risks to consumers. One year earlier, almost 3,000 patients in Kenya were affected by a falsified batch of the antiretroviral therapy Zidolam-N, used in the treatment of HIV/AIDS. And in 2009, counterfeits of a traditional anti-diabetic medicine killed two and hospitalized nine in China before it was determined that the fraudulent drug contained six times the normal dose of glibenclamide, a chemical used to lower blood sugar¹.

Isolated incidents? Sadly, no. Instead, according to world health officials, this is just the tip of the iceberg as falsified and counterfeit drugs take on a life of their own in burgeoning grey markets and increasingly slip into the legitimate supply chain.

Diagnosis: History and Scope of the Problem

According to the World Health Organization (WHO), the prevalence of *spurious, falsely-labelled, falsified, or counterfeit medicines*, or SFFC medicines as they are known – medicines that are deliberately and fraudulently produced, packaged and/or mislabeled – is a growing trend worldwide which threatens both patient safety as well as public confidence in the health systems and regulatory bodies designed to provide oversight and control.

SFFC medicines are found everywhere in the world. They range from random mixtures of harmful toxic substances to inactive, ineffective preparations. Some contain a declared, active ingredient and look so similar to the genuine product that they deceive health professionals as well as patients. But in every case, the source of a SFFC medicine is unknown and its content unreliable. SFFC medicines are always illegal. They can result in treatment failure or even death. Eliminating them is a considerable public health challenge².

¹"Medicines: spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines", World Health Organization, Fact sheet No.275, May 2012

²Ibid.



About Counterfeit Drugs

First identified as an issue in the mid-1980s when counterfeiters began reproducing soft “lifestyle” drugs used to combat obesity and baldness, etc., the replication of mass market prescription drugs such as birth control, medications for erectile dysfunction, diabetes, hypertension and high cholesterol as well as vaccines, antibiotics and antimalarials soon followed.

More than 25 years later, the scope of falsified drugs has mushroomed to include high-value drugs in high demand as well as life-saving drugs used to treat cancer, HIV/AIDS, serious cardiovascular disease and even those used to support organ transplants. None of today’s drugs or therapeutic treatments is exempt from unauthorized replication. Targeted medicines now include both branded and generic drugs and run the full gambit – everything from low-cost generic painkillers and antihistamines to high-value blockbuster drugs and specialty medicines used to treat life-threatening conditions. Even injectables and medical devices have not been spared.

According to WHO statistics³ collected in 2000:

- 32.1% of identified counterfeit drugs contained no active ingredient
- 20.2% had incorrect quantities of active ingredients
- 21.4% contained the wrong ingredients
- 5.6% had correct ingredients, but fake packaging
- 8.5% contained high levels of impurities
- 1% were copies of an original product

The impact on patients from using fraudulent drugs can range dramatically: from failure to treat minor symptoms to failure to treat critical illnesses to drug resistance caused by long-term exposure to reduced amounts of active ingredients to death. Each year between 100,000⁴ and as many as 1 million⁵ people die from counterfeit drugs according to varying statistics. Produced in sub-standard facilities with little to no quality control, these fraudulent medicines contain an array of questionable ingredients including, among other things, caffeine, rat poison, starch, chalk, gypsum, flour, sugar and even acetaminophen, used to lower fevers and promote the belief that the drug is working.

³World Health Organization, “General information on counterfeit medicines”, 2000

⁴Bate, Roger, “The deadly world of falsified and substandard medicine”, American Enterprise Institute, October 15, 2012

⁵Southwickz, Natalie, “Counterfeit Drugs Kill 1Mn People Annually: Interpol”, InSightCrime.org, October 24, 2013.

In 2013, for instance, through joint international law enforcement and the efforts of almost 100 countries, over 10 million potentially dangerous medicines worth some \$36 million were seized, resulting in 213 arrests worldwide.

Prevalence and Geographical Reach of Counterfeit Drugs

In today's globalized pharmaceutical industry, it is thought that 10% of all drugs distributed globally are counterfeit. An estimated 80% of these counterfeits are produced overseas, with China and India identified as the leading suppliers. Worldwide sales of counterfeit drugs are estimated by WHO to be in excess of \$75 billion annually, with some sources approximating annual market value to be as high as \$200 billion. As one might expect, accurate data is hard to come by.

Developing nations have historically been prime targets for counterfeits, in part because of a weaker import and regulatory infrastructure, but also due to sheer economics and the inability of large populations to widely access expensive drugs. While Asia, with over 60% of the world's population, currently represents the largest market for counterfeits, Africa, Latin America and politically and economically destabilized regions are all similarly attractive targets for those distributing rogue products. Based on WHO estimates, approximately 30% of the drugs distributed in these geographies are counterfeit. Some estimates for specific countries are as high as 60%. Adding to this, the growth of Internet-based commercial drug sales – both for products destined to as well as those emanating from developing nations – has merely exacerbated the problem.

In industrialized nations like the U.S., Canada, most EU countries, Australia, New Zealand and Japan – where median income is higher, where the pharmaceutical supply chain is better protected by stronger customs, import and regulatory oversight,

and where law enforcement is more aggressive – the occurrence of counterfeiting is statistically reduced to 1% or less.

Although the percentage may seem negligible, actual numbers help to put the situation into better perspective. In the United States alone, more than 4 billion prescriptions were issued in 2011, equating to over 40 million prescriptions that were filled using counterfeit medicines. A survey conducted in 14 European countries by Pfizer in 2010 estimated that more than €10.5 billion (U.S. \$14 billion) was spent each year on illicitly-sourced prescription drugs including those used for weight loss, influenza and erectile dysfunction; many of these drugs were counterfeit. The study further noted that the number of counterfeit drugs uncovered at EU borders increased from 560,598 articles in 2005 to 4,081,056 in 2007⁶.

By all accounts, the situation promises to intensify and although global recognition of the problem now exists, controlling it has been daunting. In 2013, for instance, through joint international law enforcement and the efforts of almost 100 countries, over 10 million potentially dangerous medicines worth some \$36 million were seized, resulting in 213 arrests worldwide.

In addition, almost 14,000 websites hosted by illegal online pharmacies were identified and shut down and more than 530,000 packages were inspected by customs and regulatory authorities. Of these, almost 42,000 packages – containing everything from antibiotics, cancer medication and anti-depressants to erectile dysfunction medication and dietary supplements – were seized⁷.

⁶Grogan, Kevin, "One in five Europeans buying fake drugs – Pfizer survey", PharmaTimes online, February 16, 2010

⁷"Counterfeit Drugs: Fighting Illegal Supply Chains", a report by Lev Kubiak, Director National Intellectual Property Rights Coordination Center, Homeland Security Investigations, U.S. Immigration and Customs Enforcement, February 27, 2014

Prevention: Technological and Regulatory Countermeasures

With the escalation of drug counterfeiting in the mid-1990s, a number of technological, regulatory, industry-driven and national initiatives were launched to help combat the problem. Clearly it must continue to be a collective effort if inroads are to be made in controlling the occurrence of counterfeit drugs.

Packaging Innovation

Over time, pharmaceutical packaging has evolved to provide better protection for both product and patient. In the past decade, steps were taken to securitize and authenticate pharmaceuticals initially by adding visible and/or hidden security features such as hologram labels and other brand protection features to the packaging. Although these measures provided some deterrents, those same technologies have also fallen prey to counterfeiting and, as such, have not successfully eliminated the problem in any meaningful way.

The newest technologies now being utilized include 2D barcodes applied directly to the packaging which retain considerably more data than previous barcodes, and Radio Frequency ID (RFID) tags which create an electronic record of chain of custody from point of manufacture to point of dispensing. While many pharmaceutical companies are already using forms of these technologies, pending regulatory changes are slated to move these solutions into the global supply chain in the coming years, with more onus being put on the verification of individual medicines at the patient dispensing level.



According to recent WHO studies:

- Some 10% of all pharmaceuticals distributed world wide are counterfeit
- Between 30% and 60% of drugs distributed in developing countries are counterfeit
- Approximately 1% of counterfeit drugs have penetrated the supply chain in developed countries
- Over 50% of drugs purchased online from sites that conceal their physical addresses are counterfeit
- Worldwide sales of counterfeit drugs is in excess of \$75 billion annually

International Collaboration

In 2006, the International Medical Products Anti-Counterfeiting Task Force (IMPACT), a partnership involving 193 WHO Member States, a variety of international and non-governmental organizations, law enforcement agencies, pharmaceutical manufacturing associations and drug and regulatory authorities was formed. Its mandate has been to work with countries and the industry to better detect and safeguard against the widespread distribution of fraudulent drugs and to minimize criminal activity through stronger and more collaborative international law enforcement.

Regulatory Reform

On a regional basis and as might be expected, the U.S. and the EU are leading the way with regulatory solutions to help circumvent the problem.

Falsified Medicines Directive (2011/62/EU)

The European Commission's Falsified Medicines Directive (2011/62/EU) was written into law in 2011, amending former legislation aimed at preventing falsified medicinal products from entering the legitimate supply chain. This legislation strengthens controls and checks on products moving through the supply chain and includes stricter controls on the sourcing of active product ingredients and excipients, especially those originating from non-EU countries.

It also calls for new or extended obligations on the part of importers and distributors of active substances, brokers, product manufacturers and wholesalers while mandating legal online pharmacies to display a common EU-wide logo on company websites. An additional requirement now demands that an obligatory authentication and safety feature appears on the outer packaging (unique pack identification).

Member states were required to transpose the directive into national law by January 2, 2013 while provisions related to the importation of active substances from third countries came into effect July 1, 2013. Specific legislation on the implementation of safety features (unique identifier) is due in 2014, with mandatory application of this identifier and medicinal product verification expected in the EU by 2017.

In anticipation of upcoming regulatory changes, two product verification initiatives are already in use in Europe. The European Stakeholder Model (ESM) is a cloud-based point-of-dispensing verification system that uses 2D data matrix barcodes to authenticate medicines and ensure that patients are receiving a genuine product. Data matrix codes are affixed by the manufacturer (if necessary, the product is verified and repackaged by the parallel distributor with a new number) and then uploaded to a central European database. This number may also be verified by both the wholesaler and pharmacy. Data includes the product number, batch number, expiry date and a unique serial number, with unregistered codes sending an immediate alert that the product may have been falsified. This system will be overseen by the European Medicines Verification Organization (EMVO), a non-profit organization that will manage the European Hub which links national systems throughout Europe. Launched in 2012, the system has been successfully tested in Sweden. Germany's securPharm verification system was integrated with the ESM model in 2013 and the proposed European Hub is expected to be fully operational by mid-2014.

Also launched in 2012, the European Directorate for the Quality of Medicines and Healthcare (EDQM) eTACT program is similarly a track-and-trace system that relies on unique identification numbers adhered to individual packaging to verify the authenticity of a medication. This number is affixed by the manufacturer and can be used by all legitimate supply chain members to verify the product. A final verification must be performed at the dispensing location. Unique to this system, however, patients themselves are able to trace

The DQSA is a progressive law that has many milestones which must be met by the pharmaceutical industry, with the end goal of having a full traceability solution in place by 2023.

and verify the safety of the medication, potentially strengthening public confidence. EDQM is a public, inter-governmental organization that promotes quality standards for the safe use of medicines worldwide.

Drug Quality and Security Act (DQSA)

In the U.S., the newly-enacted Drug Quality and Security Act (DQSA) was signed into law in November 2013 by President Obama, effectively preempting all existing state laws and regulations related to pedigree. The DQSA is a progressive law that has many milestones which must be met by the pharmaceutical industry, with the end goal of having a full traceability solution in place by 2023. The federal DQSA aims to incorporate drug transactional information into a new electronic traceability system that will allow health systems, hospitals and pharmacies to trace prescription drugs through the supply chain.

Required transactional information will include the name of the drug, its strength, quantity, dosage, National Drug Code (NDC), lot number, container/packaging size, date of transaction, date of shipment and name and address of both shipper and consignee, all of which will provide additional business value. Included in the legislation are federal licensure standards for third-party logistics providers (3PLs) and wholesale distributors. In addition, manufacturers will be required to apply a 2D barcode that contains a product identifier, serial number, lot number and expiration date by November 2017. Wholesaler drug distributors must follow suit by November 2019 and dispensers by November 2020. The full traceability solution is set to be implemented by November 2023.

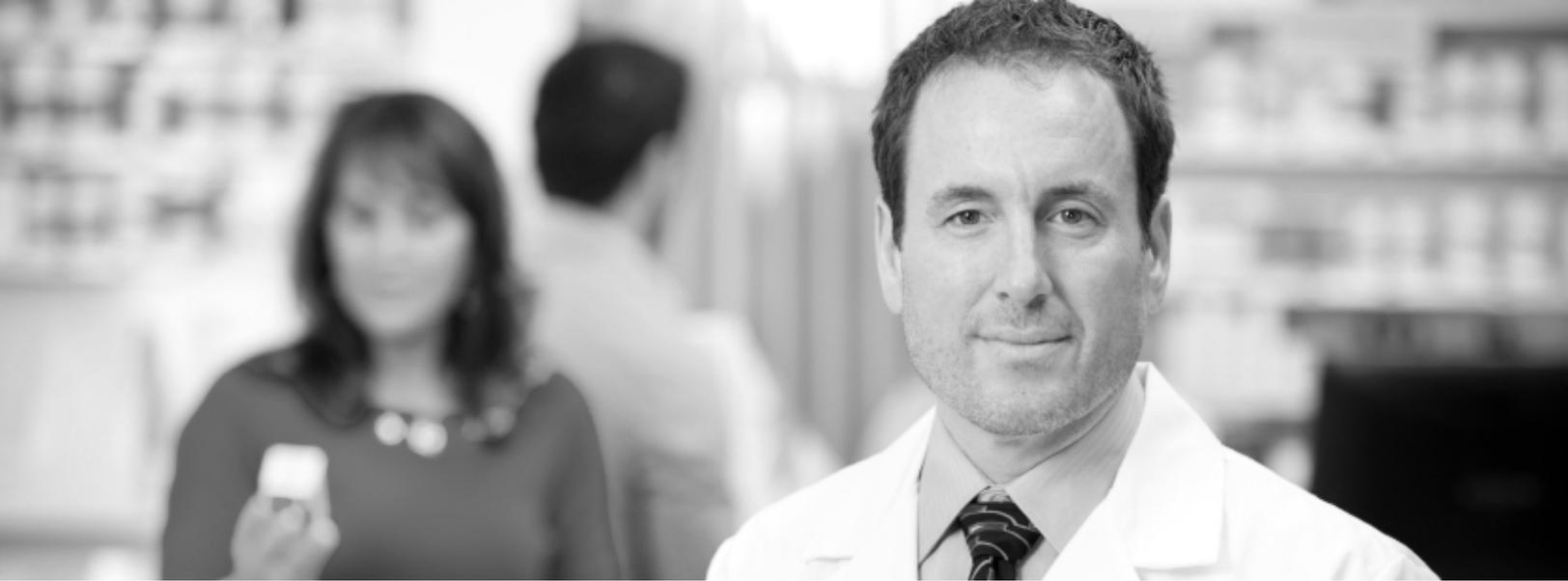
National Initiatives

At the international level, countries are implementing their own strategies to combat the growing threat of counterfeit drugs.

China is the world's top producer of both legitimate and counterfeit drugs. In 2001, the existing Drug Administration Law of the PRC was amended to increase penalties on the production and sale of falsified drugs. Since then other laws have been enacted to control counterfeit activities by regulating API manufacturers, for instance, a key to controlling counterfeit activities. While the State Food and Drug Administration (SFDA) has also increased routine inspection and sampling as well as enacted new labeling laws, enforcement remains weak and the system cumbersome. Technological solutions including 2D data matrix bar-coding and RFID tags remain expensive to implement.

As one of the world's top manufacturers of generic and patent drugs, India has taken steps to limit counterfeit drug production nationally following a 2005 estimate that some 75% of falsified drugs distributed globally have some origins in that country⁸. Although this estimate has been hotly disputed and never proven, India's Directorate General of Foreign Trade (DGFT) amended labeling requirements in 2011, making it mandatory for every drug manufactured in that country designated for export to bear a Unique Product Identification Code (GTIN) as well as 1D or 2D bar-coding on primary, secondary and tertiary packaging.

Meanwhile in Africa, the newly launched mPedigree Network, an SMS-based technology developed by



Ghanaian entrepreneur Bright Simons, began its roll-out in Nigeria in 2013 when the system became accessible to over 50 million mobile subscribers. The technology allows patients to authenticate their medicine by sending a free text message to a special hotline and receiving an immediate OK or NO response. The reply is accompanied by the name of the medication and a picture of the packaging for visual comparison. Patients need only scratch off a panel on the prescription packaging to reveal the unique ID number. This technology is now being tested in Ghana and being considered by other African states. Patients in Africa have been highly vulnerable to the negative effects of counterfeit drugs, with as many as 700,000 deaths per year linked to sub-standard malaria drugs and tuberculosis vaccines.

Moving Forward

The cost associated with counterfeit drugs is staggering – both in human and commercial terms. In some cases, patients are deprived of treatment for diseases and conditions that range from mild to severe to life-threatening. In other cases, they are harmed by dangerous substances in the product, or become resistant to traditional therapeutic treatments or vaccines. In all cases, the public loses confidence in the companies that develop these drugs and in the very agencies that have been established to protect them.

For the pharmaceutical industry, the prevalence of counterfeit drugs can represent loss of reputation, loss of valuable R&D efforts and intellectual property, loss of revenue and increased costs. Many companies, for instance, now operate their own anti-counterfeit units to police their product lines and reduce the impact of counterfeiting on the organization. Despite these efforts, the growth of counterfeit drugs is only expected to increase within the parameters of a globalized industry, especially as the cost of healthcare spirals worldwide.

What can pharmaceutical professionals do to ensure that their organizations and the patients they serve are not impacted by counterfeit drugs? The answer is to identify their highest risk products and shipments and to secure their supply chain to the fullest extent possible.

In the falsified Avastin case referenced at the beginning of this article, it was later found that the vials were sourced in Turkey and shipped to Switzerland, then Denmark and finally to the U.K. before being exported to a U.S. wholesale distributor hired by a Canadian company which was ultimately owned by an online retail pharmacy. In another case, counterfeit product was slipped into an existing shipment of legitimate drugs destined for a hospital simply by adding an extra zero to the unit count on the paperwork. In yet another case, a legitimate shipment of temperature-controlled drugs was hijacked, with the product later re-introduced into the supply chain without the benefit of quality assurance.

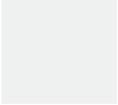
⁸Lal, Neeta, "Fake drugs a bitter pill for India", Asia Times online, June 7, 2008.

Identifying High Risk Shipments

Virtually every medicinal product is a target in today's world. Although all pharmaceutical shipments are important, pharmaceutical professionals should evaluate the severity of risks associated with a specific product prior to shipping, and consider prioritizing its journey through the supply chain as required.

Questions to consider include:

- Who is the targeted patient group? Is it an at-risk group like infants or the elderly who are more susceptible to a counterfeit product?
- How will the drug be used? Will it be used to treat a chronic condition? Does a single dose have the potential to kill?
- How is it administered? By a healthcare professional? By the patient?
- What is the patient impact if the medication contains no active ingredient? An excess of active ingredients?
- Does the product require cold chain handling to maintain stability/efficacy?
- How much annual revenue does the product generate? What role does it play in the product portfolio?
- Is the product a flagship brand? A blockbuster?
- How attractive is the product to counterfeiters (i.e. high unit price? Product shortage? High volume usage?)
- What region is the shipment destined for? What regional risk factors exist with respect to counterfeit drugs?
- Does the provider offer a full suite of services (i.e. packaging, temperature control, transport, storage, local delivery), or will services be handled piecemeal by multiple suppliers?
- Does the provider have experience/expertise in managing high-value pharmaceutical shipments? What type of track record/reputation does he have with clients, airlines, regulatory and customs agencies?
- Is the scope of operation global or regional?
- Does the company employ staff worldwide or utilize the services of third-party providers? If the latter, what specific locations are not managed by company employees? Do these destinations appear in your distribution portfolio?
- Do operatives in all locations act in strict accordance with documented company-wide SOPs?
- Is the organization GxP-compliant in all locations, or in select locations? ISO certified?
- Is there a quality management/quality assurance policy and team in place?
- Does it function independently from the operational side of the organization?
- How is quality oversight managed in the field? Is there an SOP for incidence reporting?
- Are suitable security procedures in place with respect to employee verification and screening?
- Are all security procedures and verification consistent in all locations?
- Can the service provider clearly demonstrate that policies and practices are enacted rigorously and consistently from origin to destination for each elected locations?



The best strategy to ensure full supply chain compliance is by partnering with and building a long-term relationship with a single closed-loop logistics provider able to manage all aspects of the transport and storage of bulk high-value pharmaceutical shipments worldwide.

Tightening the Supply Chain

As today's global pharmaceutical supply chain grows increasingly longer and more complex, each link provides added opportunity for counterfeiters. While pending regulatory changes promise to tighten the supply chain with respect to production and distribution entities and new packaging technologies will make the identification of counterfeit products easier, the logistics of global distribution remains a weak link. How can the pharmaceutical shipper ensure the security of the supply chain over thousands of miles and extended periods of time when the product is no longer in his possession?

The best strategy to ensure full supply chain compliance is by partnering with and building a long-term relationship with a single closed-loop logistics provider able to manage all aspects of the transport and storage of bulk high-value pharmaceutical shipments worldwide.

Benefits include:

- Enhanced control from a proven, trusted source
- Clear chain of custody at all points during transit
- Elimination of unnecessary third-party risk
- Local representation and accountability in complex and often unpredictable geographies

By utilizing the services of a GxP-compliant logistics supplier, pharmaceutical shippers can automatically ensure that they conform to all current regulatory requirements as they relate to the transport of their high-value pharmaceutical products. Equally important, they can be assured that the same standard operating procedures (SOPs) are employed worldwide to ensure product security to the greatest extent possible.

Shippers may also consider utilizing a local warehousing solution in emerging or strategic locations to reduce the costs and peril associated with multiple bulk shipments and to shorten distribution timelines. A fully-integrated logistics provider able to accommodate packaging, cold chain, transport, storage and local in-country or regional distribution is a practical solution for maintaining security in challenging locations.

As a word of caution, however, all logistics providers are not created equal, so pharmaceutical shippers should be prepared to carefully qualify all contenders.

Identifying a logistics provider with trained staff, a well-maintained infrastructure and network-wide processes in place at the global level will go a long way toward securing the supply chain and protecting the interests of both the pharmaceutical company and its patients, particularly in those areas of the world at greatest risk or where local representation is lacking.

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