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COUNTERFEIT MEDICINES

Counterfeiting of medicines is increasing, is often linked to other criminal activities and poses risks to public health. It exposes people to medicines of unverified quality, safety and efficacy. This POSTnote considers the extent of the global counterfeit medicine trade, its impact in the UK and the technologies and policy options available to combat it. It also examines the risks and benefits of online pharmacy, one of the main ways in which counterfeits are distributed.

Background

Counterfeiting is a high-volume, high-profit business which poses health risks, infringes intellectual property rights, medicines legislation and other aspects of criminal law. Indirect impacts are lost revenue for pharmaceutical companies, brand damage and decreased public confidence. Counterfeit medicines and devices circulate globally via unregulated channels (including unauthorised online pharmacies) but can also enter legitimate drug supply chains. It can be difficult to distinguish them from genuine products (Fig 1). The World Health Organisation (WHO) classes medicines as counterfeit if they:

- are fraudulently packaged or mislabelled with respect to identity and/or source (for example if they are not made by the genuine manufacturer);
- contain no active ingredient, incorrect quantities or an undeclared active ingredient;
- are contaminated with other materials (chalk, boric acid, lead and rat poison are typical examples);
- are past their expiry date;
- contain no or incorrect patient information leaflets.

Counterfeits often display more than one of these features. A study of 286 incidents showed that 67% had both counterfeited drug and packaging, 28% had counterfeit drug and 5% had counterfeit packaging only.

Extent of Counterfeit Medicines

While counterfeiting of branded and generic (copies of out-of-patent drugs) medicines is increasing in volume and range, there are few comprehensive analyses of global statistics due to varied definitions of counterfeits between legislatures, and the level and frequency of monitoring. Data are collected by governments and pharmaceutical industry activities, often in collaboration. Counterfeits pose a greater problem in countries where manufacture and supply of drugs are less regulated and where enforcement is weak. Estimates indicate that:

- in wealthy countries like the UK with strong regulatory frameworks (Box 1), counterfeits are likely to account for ~1% of the total medicines market, but an estimated 50% of drugs sold online are fake;
- in emerging economies, the proportion is 10% but in the former Soviet republics it can be as high as 20%;
- in Latin America, South East Asia and Sub-Saharan Africa an estimated 30% of medicines are counterfeit.[2]

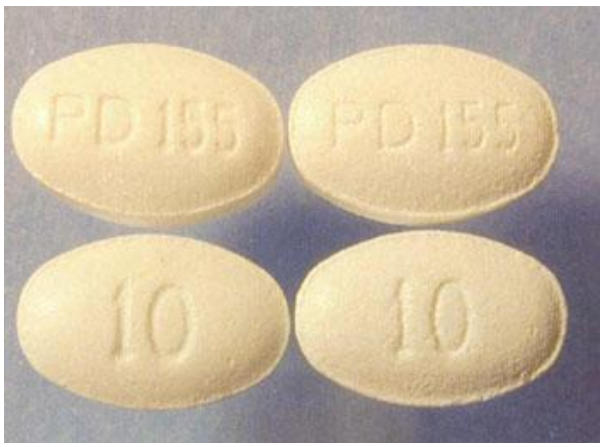

Figure 1. *Distinguishing genuine (right hand side) and counterfeit tablets (and packaging) apart on visual inspection is difficult (image courtesy of Pfizer). In 2005, a counterfeit version of this cholesterol-lowering drug was found in the UK. 120,000 packs were recalled from 240 pharmacies; 60% were counterfeit.*[1]

Data collated by the Pharmaceutical Security Institute report that the number of unique incidents increased annually from 196 in 2002 to 1,834 in 2008.[3] The global reach of a counterfeit made in one location can be significant: drugs made by a producer in China were found in 42 countries.[4] EU borders and customs agencies have targeted illegal medicines, seizing 2.7m items in 2006. A two-month action in 2008 (MEDI-FAKE) led to seizure of 34m illegal medicines, including antibiotics, erectile dysfunction tablets and chemical precursors used in manufacturing.[5]

Box 1. Safeguarding the UK Drug Supply Chain
The UK government's Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for ensuring that medicines are safe and effective. Its Enforcement and Intelligence Group investigates suspected counterfeiting in the regulated and unregulated supply chains. If the MHRA identifies a public health risk, it issues an alert (classified from 1 (most critical) to 4 depending on risk) and the drug is withdrawn. Class 1 alerts arise from medicines being contaminated, mislabelled or containing incorrect ingredients and require immediate recall. The MHRA has a 24 hour hotline for reporting counterfeits and encourages all agencies (police, pharmaceutical companies, customs, trading standards and pharmacies) and individuals (health professionals and the public) to report suspect drugs.

Manufacture of Counterfeits
Recent seizures at EU borders show that 60% of drugs originated from China, where counterfeiters focus on high-value, in-demand drugs. Raids on premises show that production often occurs in unsanitary conditions, using rudimentary equipment and cheap labour to mass-produce tablets and packaging. The UK is not a major location for manufacturing counterfeits, but is a large market for sale and transit with seizures traced to production in the Far East and Indian sub-continent.

Types of Counterfeit Medicines in Circulation
The classes of drugs most commonly counterfeited are genito-urinary, anti-infectives and central nervous system medicines but piracy of other categories is increasing. A variety of counterfeit medicines has been seized in the UK including treatments for erectile dysfunction, hair loss, obesity and pain relief (Box 2). Life-saving drugs for blood pressure and cancer, and also anti-psychotics and statins are now appearing. Medicines seized in the UK often contain reduced amounts of the active ingredient and all included impurities and failed to meet standards required by Good Manufacturing Practice regulations. The UK has had nine known cases of counterfeit prescription-only medicines (POMs) reaching the legal supply chain since 2004. In an incident in 2008, 72,000 packs of counterfeit heart and cancer medicines led to four recalls. The MHRA points out that this is in the context of 800 million prescriptions issued annually. There are no reliable statistics on the number of counterfeits reaching consumers through unregulated sources, such as illegal online pharmacies.

Consequences of Counterfeit Medicines
Public Health and Patient Safety
Counterfeits containing sub-therapeutic levels of active ingredients pose a significant health risk to patients taking medicines to manage life-threatening conditions. Counterfeit formulations may be metabolised differently, so even if an active ingredient is present, it may not be taken up by the body. Health can also be compromised if counterfeits contain toxic substances such as heavy metals. No fatalities have been attributed officially to counterfeits in the UK but have been reported elsewhere (including Canada, but mostly in the developing world). It is unclear whether the UK coroners' system is well-placed to detect the involvement of counterfeits.

Box 2. Counterfeits in the UK Legal Supply Chain
The MHRA recalls suspect medicines, alerting hospitals and pharmacies to remove the items, or to retrieve them from patients once dispensed. It has issued nine recalls since 2004 for counterfeits that reached pharmacies and patients through the legitimate supply chain.[1] Four batches were intercepted at wholesale level and one in a clinical trial. Medicines often contained insufficient active ingredients and had been repackaged into English cartons via parallel trade (Box 3). They included:
- **cardio-vascular disease** - counterfeit Plavix (inhibits blood clots) was recalled from pharmacies in 2007.
- **prostate cancer** - counterfeits of Astra Zeneca's Casodex reached patients in 2007. The packets bore genuine Astra Zeneca lot numbers; the original lots bearing these numbers were supplied to France.
- **anti-psychotics** - counterfeits of Eli Lilly's drug Zyprexa bore genuine lot numbers and reached patients triggering a Class 1 recall.
- **cholesterol** - counterfeits of Pfizer's drug Lipitor reached pharmacies in 2005 and 2006. The Class 2 recalls issued also had to apply to authentic products since genuine lot numbers were used on the fakes.
- **obesity** - counterfeits of Abbott's anti-obesity drug Reductil reached patients in 2004.

Using online pharmacies poses indirect health risks. Men are less likely to consult a doctor than women and more likely to buy medicines online. Men buying POMs (such as for erectile dysfunction) from illegal online pharmacies may risk their health in two ways. Firstly, the drug may be counterfeit. Secondly, a man consulting a GP about erectile dysfunction would be assessed for the risk of cardiovascular disease and stroke, since the conditions may be linked. A man buying online would forgo this assessment and so miss out on opportunities for other diagnoses, with consequences for long-term health.

Non-health Related
Indirect impacts of counterfeiting include intellectual property infringements and economic impacts on industry from lost sales and brand damage; such commercially sensitive information is not available. There are few analyses of economic losses, but estimates of the market value of seized medicines in the UK since 2004 amount to £6.5m. Sales from unauthorised online sources exceed this figure by a significant margin, estimated by one survey at $12bn a year worldwide in 2008.

Incentives to Counterfeit Medicines
Several factors make this activity attractive to criminals:
- free trade zones, globalisation and complex medicine supply chains make it easy to introduce counterfeits into legitimate supply channels, especially in areas with weak drug regulatory controls.
- it is a lucrative activity, especially for drugs that command high prices or are required in large volumes.
- technology to make constituent ingredients and packaging is cheap and readily available.
- the Internet provides counterfeiters with ready access to markets outside regulated medicine supply chains. Current legislation and regulation do not provide a strong enough deterrent, through both enforcement and penalties, to discourage counterfeiters.[4]

Complex Medicine Supply Chains

Medicine distribution in the EU is complex. Historically, medicines passed from the manufacturers to patients via wholesalers but now many legitimate intermediates are involved, including wholesalers, brokers and parallel traders. Parallel trade (Box 3) is international import of goods, occurring when versions of drugs are made for sale in different markets or when the same drug is priced differently (UK prices are among the highest in the EU). It stimulates competitive pricing of patented medicines but has been blamed for shortages. The British Association of Pharmaceutical Wholesalers (10 wholesalers supply 90% of the UK's medicines) estimates that parallel traded medicines account for 13% of total UK drug sales, valued at £9-10bn. Such a large, complex, supply chain is difficult to secure. It is almost impossible to track a medicine (in the case of a recall for example) to its origins when it has passed through multiple handlers in numerous countries. Some companies believe that EU regulatory and enforcement capability has not kept pace with increasingly complex medicine trading mechanisms. Pfizer has responded to this by supplying UK pharmacies directly. Such schemes bypass intermediaries; other companies may follow suit.

Box 3. Parallel Trading in Medicines

Parallel traded medicines are purchased in one country and then legally repackaged and/or relabelled and sold elsewhere at a higher price. A single box of tablets may be handled by numerous intermediates before reaching the end user. Parallel trading is regulated by the European Medicines Agency and the MHRA. Repackaging and re-labelling is inspected by the MHRA but import and distribution takes place outside the original manufacturer's supply chain. Pfizer estimates that the number of parallel importing licences granted for one of its products rose from 62 to 660 in 2006.

Measures to Tackle Counterfeiting

Pharmaceutical Industry

Industry tackles counterfeiting in three main ways:

- investing in overt and covert technologies to secure medicine packaging and supply chains (see Box 4);
- investigating suspected counterfeit rackets and working with government agencies in and outside the UK to bring civil claims or criminal prosecutions;
- funding awareness campaigns to educate healthcare professionals and the public about the dangers.

Adopting the technologies described in Box 4 is widely supported, but raises issues of costs and agreement on a harmonised system for use in the global supply chain. Pharmaceutical companies test drugs to identify counterfeiting of their brands. This involves examining packaging and forensic analysis of suspicious products. Companies bring prosecutions under civil law, to recover assets acquired through criminal activity. Others work with national agencies to instigate criminal proceedings.

The International Policy Response

The WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) is a coalition of 193 countries set up to promote international collaboration and to publish guidelines for developing national strategies (on legislation, enforcement, use of technology and sharing intelligence). It runs a web-based counterfeit reporting system and works with international agencies, notably Interpol, the Permanent Forum on International Pharmaceutical Crime and the World Customs Organisation. They co-ordinate operations and train police and officials from customs and drug regulatory agencies in counterfeit sample handling and identification. Initiatives between IMPACT and Interpol have included "Internet days of action" to target illegal online sales as well as longer operations in 2008:

- **Operation Mamba** raided 45 premises in Tanzania and Uganda and seized ~100 types of suspect medicines including anti-malarials and anti-fungals.
- **Operation Storm** in south-east Asia targeted manufacturers/distributors of medicines identified as a health risk (for pneumonia and childhood-related illnesses). After 200 raids, 16m tablets were seized.

Box 4. Anti-Counterfeiting Technologies

Packaging technologies deter counterfeiters and alert users to medicines of dubious origin. The optimum place for overt security measures is at the point of use by the patient. Some technologies currently used include specialised printing and security inks, blister packs, hi-tech holograms, watermarks and tamper-evident packaging. Even the most sophisticated holograms can be copied to look convincing to consumers. However, importing and repackaging medicines through legal parallel trade often renders such measures ineffective.

Supply chain management such as track and trace technologies use unique identification numbers (for batches and individual packets) to register product authenticity against a database. Other technologies include 2-D barcodes, similar to standard black and white barcodes but with greater data storage capacity to include origin, lot number and expiration date. Radio Frequency Identification (RFIDs) tagging, used by retailers for stock control has been trialled by the US Food and Drug Administration. It advocates phasing them into the medicine supply chain. Some US companies tag 'at-risk' products. Others supply pharmacies directly, which is complex and costly, but may be necessary to protect revenue. There are concerns that this may lead to shortages. Where several wholesalers provide medicines, one can step in if another cannot fulfil an order.

The European Policy Response

The European Commission outlined proposals to tackle counterfeiting in 2006, and is likely to approve a Directive on falsified medicines in 2010. Proposals aim to prevent counterfeits entering the supply chain by:

- using mandatory safety features (such as individual product codes or seals) for medicines deemed 'high risk', affixed by authorised manufacturers and replaced under strict conditions, allowing identification and authentication by all involved in distribution.
- more rigorous certification and inspection of wholesalers, including audits and listing in a database kept by the European Medicines Evaluation Agency.
- tightening requirements for import of medicines and active pharmaceutical ingredients from outside the EU and improvement of inspections and enforcement.

The Directive is welcomed by industry although there is no agreement on which security features should be used or on how a system could be harmonised in the EU. It is

unlikely that any system would be operational before 2012 and unclear which medicines will be classed as "high risk" and whether this will cover all generic medicines. The European Federation of Pharmaceutical Industries and Associations is concerned that introducing variable standards will result in less protected medicines being targeted and wants the same standards applied to all POMs. Critics argue that the proposals will succeed only if member states allocate adequate resources to enforce them and there are steps to tackle counterfeiting outside Europe, where most production occurs. The EC will expect member states to "monitor" online sales and take legal action against those selling illegal products.

The UK's Policy Response

The MHRA's anti-counterfeiting strategy aims to make the UK a less attractive market to counterfeiters.[6] The agency is seeking to raise tariffs for offences and a consultation on strengthening policy closes in March 2010. It keeps a watch list of high-risk medicines to inform intelligence and participates in international initiatives. It has prosecuted offenders for crimes ranging from illegal advertising to global counterfeiting rings. Investigations are complex, especially when international networks target weaknesses in national and international supply chains. Recently, several prosecutions for distribution have been brought. Sentences ranged from a £1,000 fine to 6 years' imprisonment. The MHRA co-operates with police, Customs and Excise and Trading Standards to prosecute using:

- the Medicines Act, where the maximum sentence is 2 years imprisonment and/or an unlimited fine;
- the Trade Marks Act and Proceeds of Crime Act with maximum sentences of 10 and 14 years respectively.

Internet Pharmacies and Counterfeits

Online pharmacy offers improved access, choice and convenience. Some value online anonymity over the possible risks of buying a counterfeit, particularly for embarrassing conditions (Box 5). The European Alliance for Access to Safe Medicines (EAASM) estimates that 62% of websites concealing their physical address supply counterfeits. It warns that buying from unauthorised sources increases the risk of being supplied with them. Several UK chains have legitimate online services to supply over-the-counter and POMs but counterfeiters exploit the online marketplace by producing sophisticated websites that appear legitimate. They use **search engine advertising** and **spam emails** to increase web traffic to online stores. Dubious sites sell counterfeit POMs without professional advice or checks on their quality and effectiveness. There is no legal recourse should problems arise. Surveys in the US of brand infringement for six POMs found 110,000 fraudulent sites and 2,986 online pharmacies. Most were hosted in the US, China and Russia (12% in the UK). Estimates of annual sales through such sites increased from $4bn to $12bn from 2007 to 2008. Sites rarely required a prescription, declared fake accreditation or sold drugs at significant discounts compared with genuine sources. Users' details were at risk since many sites did not secure transactions. Websites hosted outside the UK are not regulated by the MHRA. The EAASM proposes that internet search and credit card companies could bar unauthorised sites from search results and impose extra checks on transactions.[7] There is concern that health professionals lack awareness of the risk from counterfeits and cannot advise patients on how to protect themselves from disreputable online pharmacies or auction sites. The MHRA runs public awareness campaigns but has not yet targeted this group and there is little guidance for the medical profession from professional bodies. The Royal Pharmaceutical Society of Great Britain's accreditation scheme identifies legitimate pharmacy websites with a logo. Pfizer's ongoing publicity campaign warns of the dangers of buying from unlicensed websites. The impact of these activities has not been assessed, but it is hoped that the public will undermine the counterfeits market by buying from reputable sources and reporting suspect medicines.

Box 5. Consumer Attitudes to Online Pharmacy

Pfizer, which produces the branded medicine Viagra, surveyed 935 men aged over 35. Men were surveyed since they are much less likely than women to access healthcare services and more likely to purchase the types of medicines that are commonly counterfeited. Key survey findings were:

- 1 in 10 bought POMs online without a prescription;
- 50% purchasing medicines without a prescription did so online (67% for those buying erectile dysfunction medicines) from sites in the UK and further afield;
- men did not see this as a high risk activity;
- 60% agreed that if it were possible that their medicine was counterfeited it would influence their decision to purchase POMs through the internet.

Overview

- A wide variety of counterfeit medicines circulates globally, largely through unauthorised channels such as online pharmacies, posing a public health risk.
- The European Commission intends to strengthen medicine supply chains though a proposed Directive. This is unlikely to be enforced before 2012. Its impact on counterfeit production outside the EU is uncertain.
- The UK's Medicines and Healthcare products Regulatory Agency is consulting on policies to improve the security of the regulated national supply chain.
- Progress is being made to raise public awareness of the risks of illegal online pharmacies and counterfeits.

Endnotes

1 www.mhra.gov.uk//index.htm
2 World Health Organisation, www.who.int/en/
3 Pharmaceutical Security Institute, www.psi-inc.org/
4 OECD, *The Economic Impact of Counterfeiting and Piracy*, 2007
5 *Community Customs Activities on Counterfeit and Piracy: Results at the European Border*, EC Taxation & Customs Union, 2007
6 *Anti-Counterfeiting Strategy 2007-2010*, MHRA
7 *The Counterfeiting Superhighway*, 2008, European Alliance for Access to Safe Medicines

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POST is grateful to all contributors and reviewers. For further information on this subject, please contact Dr Sarah Bunn, at POST.

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