EMBO reports

science & society

# Elixirs of death

International organizations are working towards a global solution to address the problem of falsified and substandard medicines, but progress has stagnated

*Katrin Weigmann*

When people take medicine, they assume that it will make them better. However many patients cannot trust their drugs to be effective or even safe. Fake or substandard medicine is a major public health problem and it seems to be growing. More than 200 heart patients died in Pakistan in 2012 after taking a contaminated drug against hypertension [1]. In 2006, cough syrup that contained diethylene glycol as a cheap substitute for pharmaceutical-grade glycerin was distributed in Panama, causing the death of at least 219 people [2,3]. However, the problem is not restricted to developing countries. In 2012, more than 500 patients came down with fungal meningitis and several dozens died after receiving contaminated steroid injections from a compounding pharmacy in Massachusetts [4]. The same year, a fake version of the anti-cancer drug Avastin, which contained no active ingredient, was sold in the USA. The drug seemed to have entered the country through Turkey, Switzerland, Denmark and the UK [5].

**…many patients cannot trust their drugs to be effective or even safe**

The extent of the problem is not really known, as companies and governments do not always report incidents [6]. However, the information that is available is alarming enough, especially in developing countries. One study found that 20% of antihypertensive drugs collected from pharmacies in Rwanda were substandard [7]. Similarly, in a survey of anti-malaria drugs in Southeast Asia and sub-Saharan Africa, 20–42% were found to be either of poor quality or outright fake [8], whilst 56% of amoxicillin capsules sampled in different Arab countries did not meet the US Pharmacopeia requirements [9].

Developing countries are particularly susceptible to substandard and fake medicine. Regulatory authorities do not have the means or human resources to oversee drug manufacturing and distribution. A country plagued by civil war or famine might have more pressing problems—including shortages of medicine in the first place. The drug supply chain is confusingly complex with medicines passing through many different hands before they reach the patient, which creates many possible entry points for illegitimate products. Many people in developing countries live in rural areas with no local pharmacy, and anyway have little money and no health insurance. Instead, they buy cheap medicine from street vendors at the market or on the bus (Fig 1; [2,10,11]). "People do not have the money to buy medicine at a reasonable price. But quality comes at a price. A reasonable margin is required to pay for a quality control system," explained Hans Hogerzeil, Professor of Global Health at Groningen University in the Netherlands. In some countries, falsifying medicine has developed into a major business. The low risk of being detected combined with relatively low penalties has turned falsifying medicine into the "perfect crime" [2].

There are two main categories of illegitimate drugs. 'Substandard' medicines might result from poor-quality ingredients, production errors and incorrect storage. 'Falsified' medicine is made with clear criminal intent. It might be manufactured outside the regulatory system, perhaps in an illegitimate production shack that blends chalk with other ingredients and presses it into pills [10]. Whilst falsified medicines do not typically contain any active ingredients, substandard medicine might contain subtherapeutic amounts. This is particularly problematic when it comes to anti-infectious drugs, as it facilitates the emergence and spread of drug resistance [12]. A sad example is the emergence of artemisinin-resistant *Plasmodium* strains at the Thai–Cambodia border [8] and the Thai–Myanmar border [13], and increasing multidrug-resistant tuberculosis might also be attributed to substandard medication [11].

**Many people in developing countries live in rural areas with no local pharmacy, and anyway have little money and no health insurance**

Even if a country effectively prosecutes falsified and substandard medicine within its borders, it is still vulnerable to fakes and low-quality drugs produced elsewhere where regulations are more lax. To address this problem, international initiatives are urgently required [10,14,15], but there is no internationally binding law to combat counterfeit and substandard medicine. Although drug companies, governments and NGOs are interested in good-quality medicines, the different parties seem to have difficulties coming to terms with how to proceed. What has held up progress is a conflation of health issues and economic interests: innovator companies and high-income countries have been accused of pushing for the enforcement of intellectual property regulations under the guise of protecting quality of medicine [14,16].

The concern that intellectual property (IP) interests threaten public health dates back to the 'Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement' of the

**Fig 1** | Women sell smuggled, counterfeit medicine on the Adjame market in Abidjan, Ivory Coast, in 2007. Fraudulent street medecine sales rose by 15–25% in the past two years in Ivory Coast. Photo credit: Issouf Sanogo/AFP Photo/Getty Images.

World Trade Organization (WTO), adopted in 1994, to establish global protection of intellectual property rights, including patents for pharmaceuticals. The TRIPS Agreement had devastating consequences during the acquired immunodeficiency syndrome epidemic, as it blocked patients in developing countries from access to affordable medicine. Although it includes flexibility, such as the possibility for governments to grant compulsory licenses to manufacture or import a generic version of a patented drug, it has not always been clear how these can be used by countries [14,16,17].

In response to public concerns over the public health consequences of TRIPS, the Doha Declaration on the TRIPS Agreement and Public Health was adopted at the WTO's Ministerial Conference in 2001. It reaffirmed the right of countries to use TRIPS flexibilities and confirmed the primacy of public health over the enforcement of IP rights. Although things have changed for the better, the Doha Declaration did not solve all the problems associated with IP protection and public health. For example, anti-counterfeit legislation, encouraged by multi-national pharmaceutical industries and the EU, threatened to impede the availability of generic medicines in East Africa [14,16,18]. In 2008–2009, European customs authorities seized shipments of legitimate generic medicines in transit from India to other developing countries because they infringed European IP laws [14,16,17]. "We're left with decisions being taken based on patents and trademarks that should be taken based on health," commented Roger Bate, a global health expert and resident scholar at the American Enterprise Institute in Washington, USA. "The health community is shooting themselves in the foot."

Conflating health care and IP issues are reflected in the unclear use of the term 'counterfeit' [2,14]. "Since the 1990s the World Health Organization (WHO) has used the term 'counterfeit' in the sense we now use 'falsified'," explained Hogerzeil. "The confusion started in 1995 with the TRIPS agreement, through which the term 'counterfeit' got the very narrow meaning of trademark infringement." As a consequence, an Indian generic, for example, which is legal in some countries but not in others, could be labelled as 'counterfeit'—and thus acquire the negative connotation of bad quality. "The counterfeit discussion was very much used as a way to block the market of generics and to put them in a bad light," Hogerzeil concluded.

The rifts between the stakeholders have become so deep during the course of these discussions that progress is difficult to achieve. "India is not at all interested in any international regulation. And, unfortunately, it wouldn't make much sense to do anything without them," Hogerzeil explained. Indeed, India is a core player: not only does it have a large generics industry, but also the country seems to be, together with China, the biggest source of fake medical products [19,20]. The fact that India is so reluctant to react

is tragically ironic, as this stance hampers the growth of its own generic companies like Ranbaxy, Cipla or Piramal. "I certainly don't believe that Indian generics would lose market share if there was stronger action on public health," Bate said. Indeed, stricter regulations and control systems would be advantageous, because they would keep fakers at bay. The Indian generic industry is a common target for fakers, because their products are broadly distributed. "The most likely example of a counterfeit product I have come across in emerging markets is a counterfeit Indian generic," Bate said. Such fakes can damage a company's reputation and have a negative impact on its revenues when customers stop buying the product.

The WHO has had a key role in attempting to draft international regulations that would contain the spread of falsified and substandard medicine. It took a lead in 2006 with the launch of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). But IMPACT was not a success. Concerns were raised over the influence of multi-national drug companies and the possibility that issues on quality of medicines were conflated with the attempts to enforce stronger IP measures [17]. The WHO distanced itself from IMPACT after 2010. For example, it no longer hosts IMPACT's secretariat at its headquarters in Geneva [2].

**'Substandard' medicines might result from poor quality ingredients, production errors and incorrect storage. 'Falsified' medicine is made with clear criminal intent**

In 2010, the WHO's member states established a working group to further investigate how to proceed, which led to the establishment of a new "Member State mechanism on substandard/spurious/falsely labelled/falsified/counterfeit medical products"(http://www.who.int/medicines/services/counterfeit/en/index.html). However, according to a publication by Amir Attaran from the University of Ottawa, Canada, and international colleagues, the working group "still cannot agree how to define the various poor-quality medicines, much less settle on any concrete actions" [14]. The paper's authors demand more action and propose a binding legal framework: a treaty. "Until we have stronger public health law, I don't think that we are going to resolve this problem," Bate, who is one of the authors of the paper, said.

Similarly, the US Food and Drug Administration (FDA) commissioned the Institute of Medicine (IOM) to convene a consensus committee on understanding the global public health implications of falsified and substandard pharmaceuticals [2]. Whilst others have called for a treaty, the IOM report calls on the World Health Assembly—the governing body of the WHO—to develop a code of practice such as a "voluntary soft law" that countries can sign to express their will to do better. "At the moment, there is not yet enough political interest in a treaty. A code of conduct may be more realistic," Hogerzeil, who is also on the IOM committee, commented. Efforts to work towards a treaty should nonetheless be pursued, Bate insisted: "The IOM is right in that we are not ready to sign a treaty yet, but that does not mean you don't start negotiating one."

Whilst a treaty might take some time, there are several ideas from the IOM report and elsewhere that could already be put into action to deal with this global health threat [10,12,14,15,19]. Any attempts to safeguard medicines need to address both falsified and substandard medicines, but the counter-measures are different [14]. Falsifying medicine is, by definition, a criminal act. To counteract fakers, action needs to be taken to ensure that the appropriate legal authorities deal with criminals. Substandard medicine, on the other hand, arises when mistakes are made in genuine manufacturing companies. Such mistakes can be reduced by helping companies do better and by improving quality control of drug regulatory authorities.

Manufacturing pharmaceuticals is a difficult and costly business that requires clean water, high-quality chemicals, expensive equipment, technical expertise and distribution networks. Large and multi-national companies benefit from economies of scale to cope with these problems. But smaller companies often struggle and compromise in quality [2,21]. "India has 20–40 big companies and perhaps nearly 20,000 small ones. To me, it seems impossible for them to produce at good quality, if they remain so small," Hogerzeil explained. "And only by being strict, can you force them to combine and to become bigger industries that can afford good-quality assurance systems." Clamping down on drug quality will therefore lead to a consolidation of the industry, which is an essential step. "If you look at Europe and the US, there were hundreds of drug companies—now there are dozens. And if you look at the situation in India and China today, there are thousands and that will have to come down to dozens as well," Bate explained.

**…innovator companies and high-income countries have been accused of pushing for the enforcement of intellectual property regulations under the guise of protecting […] medicine**

In addition to consolidating the market by applying stricter rules, the IOM has also suggested measures for supporting companies that observe best practices [2]. For example, the IOM proposes that the International Finance Corporation and the Overseas Private Investment Corporation, which promote private-sector development to reduce poverty, should create separate investment vehicles for pharmaceutical manufacturers who want to upgrade to international standards. Another suggestion is to harmonize market registration of pharmaceutical products, which would ease the regulatory burden for generic producers in developing countries and improve the efficiency of regulatory agencies.

Once the medicine leaves the manufacturer, controlling distribution systems becomes another major challenge in combatting falsified and substandard medicine. Global drug supply chains have grown increasingly complicated; drugs cross borders, are sold back and forth between wholesalers and distributers, and are often repackaged. Still, there is a main difference between developing and developed countries. In the latter case, relatively few companies dominate the market, whereas in poorer nations, the distribution system is often fragmented and uncontrolled with parallel schemes, too few pharmacies, even fewer pharmacists and many unlicensed medical vendors. Every transaction creates an opportunity for falsified or substandard medicine to enter the market [2,10,19]. More streamlined and transparent supply chains and stricter licensing requirements would be crucial to improve drug quality. "And we can start in the US," Hogerzeil commented.

**…India is a core player: not only does it have a large generics industry, but the country also seems to be, together with China, the biggest source of fake medical products**

Distribution could be improved at different levels, starting with the import of medicine. "There are states in the USA where the regulation for medicine importation is very lax. Anyone can import; private clinics can buy medicine from Lebanon or elsewhere and fly them in," Hogerzeil explained. The next level would be better control over the distribution system within the country. The IOM suggests that state boards should license wholesalers and distributors that meet the National Association of Boards of Pharmacy accreditation standards. "Everybody dealing with medicine has to be licensed," Hogerzeil said. "And there should be a paper trail of who buys what from whom. That way you close the entry points for illegal drugs and prevent that falsified medicines enter the legal supply chain." The last level would be a track-and-trace system to identify authentic drugs [2]. Every single package of medicine should be identifiable through an individual marker, such as a 3D bar code. Once it is sold, it is ticked off in a central database, so the marker cannot be reused.

According to Hogerzeil, equivalent measures at these different levels should be established in every country. "I don't believe in double standards", he said. "Don't say to Uganda: 'you can't do that'. Rather, indicate to them what a cost-effective system in the West looks like and help them, and give them the time, to create something in that direction that is feasible in their situation."

Nigeria, for instance, has demonstrated that with enough political will, it is possible to reduce the proliferation of falsified and substandard medicine. Nigeria had been a major source for falsified products, but things changed in 2001, when Dora Akunyili was appointed Director General of the National Agency for Food and Drug Administration and Control. Akunyili has a personal motivation for fighting falsified drugs: her sister Vivian, a diabetic patient, lost her life to fake insulin in 1988. Akunyili strengthened import controls, campaigned for public awareness, clamped down on counterfeit operations and pushed for harsher punishments [10,19]. Paul Orhii, Akunyili's successor, is committed to continuing her work [10]. Although there are no exact figures, various surveys indicate that the rate of bad-quality medicine has dropped considerably in Nigeria [10].

China is also addressing its drug-quality problems. In a highly publicized event, the former head of China's State Food and Drug Administration, Zheng Xiaoyu, was executed in 2007 after he was found guilty of accepting bribes to approve untested medicine. Since then, China's fight against falsified medicine has continued. As a result of heightened enforcement, the number of drug companies in China dwindled from 5,000 in 2004 to about 3,500 this year [2]. Moreover, in July 2012, more than 1,900 suspects were arrested for the sale of fake or counterfeit drugs.

Quality comes at a price, however. It is expensive to produce high-quality medicine, and it is expensive to control the production and distribution of drugs. Many low- and middle-income countries might not have the resources to tackle the problem and might not see quality of medicine as a priority. But they should, and affluent countries should help. Not only because health is a human right, but also for economic reasons. A great deal of time and money is invested into testing the safety and efficacy of medicine during drug development, and these resources are wasted when drugs do not reach patients. Falsified and substandard medicines are a financial burden to health systems and the emergence of drug-resistant pathogens might make invaluable medications useless. Investing in the safety of medicine is therefore a humane and an economic imperative.

CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

REFERENCES

1. World Health Organization (2013) Deadly medicines contamination in Pakistan. http://www.who.int/features/2013/pakistan_medicine_safety/en/
2. Institute of Medicine (2013) *Countering the Problem of Falsified and Substandard Drugs* (eds Buckley JG, Gostin LO), pp. Washington, USA: National Academies Press
3. Rentz ED *et al* (2008) Outbreak of acute renal failure in Panama in 2006: a case-control study. *Bull World Health Organ* **86:** 737–816
4. Gudeman J, Jozwiakowski M, Chollet J, Randell M (2013) Potential risks of pharmacy compounding. *Drugs RD* **13:** 1–8
5. Weaver C, Whaler J (2012) How fake cancer drugs entered U.S. [online]. *The Wall Street Journal* 20 Jul. htttp://online.wsj.com/article/SB10001424052702303879604577410430607090226.html
6. Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ (2005) The global threat of counterfeit drugs: why industry and governments must communicate the dangers. *PLoS Med* **2:** e100
7. Twagirumukiza M, Cosijns A, Pringels E, Remon JP, Vervaet C, van Bortel L (2009) Influence of tropical climate conditions on the quality of antihypertensive drugs from Rwandan pharmacies. *Am J Trop Med Hyg* **81:** 776–781
8. Nayyar GML, Breman JG, Newton PN, Herrington J (2012) Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis* **12:** 488–496
9. Kyriacos S, Mroueh M, Chahine RP, Khouzam O (2008) Quality of amoxicillin formulations in some Arab countries. *J Clin Pharm Ther* **33:** 375–379
10. Bate R (2012) *Phake: The Deadly World of Falsified and Substandard Medicines*. Washington DC, USA: AEI Press
11. Bate R (2013) Feeding a disease with fake drugs [online]. *New York Times* 5 Feb. http://www.nytimes.com/2013/02/05/opinion/feeding-a-disease-with-fake-drugs.html?_r=1&
12. Newton PN, Green MD, Fernández FM (2010) Impact of poor-quality medicines in the 'developing' world. *Trends Pharmacol Sci* **31:** 99–101
13. Phyo AP *et al* (2012) Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. *Lancet* **379:** 1960–1966
14. Attaran A *et al* (2012) How to achieve international action on falsified and substandard medicines. *BMJ* **345:** e7381
15. Attaran A, Bate R, Kendall M (2011) Why and how to make an international crime of medicine counterfeiting. *J Int Criminal Justice* **9:** 325–354
16. Brant J, Malpani R (2011) *Eye on the Ball Medicine Regulation—not IP Enforcement—can Best Deliver Quality Medicines*. Oxford, UK: Oxfam GB for Oxfam International
17. Clift C (2010) *Combating Counterfeit, Falsified and Substandard Medicines: Defining the Way Forward?* London, UK: Chatham House
18. Mullard A (2010) EU implicated in controversial counterfeiting bill. *Lancet* **375:** 1335
19. Bate R (2008) *Making a Killing. The Deadly Implications of the Counterfeit Drug Trade*. Washington DC, USA: AEI Press
20. The Economist (2013) Bad medicine [online]. *The Economist* 13 Oct. http://www.economist.com/node/21564546/print
21. Kaplan W, Laing R (2005) *Local Production of Pharmaceuticals: Industrial Policy and Access to Medicines—An Overview of Key Concepts, Issues and Opportunities for Future Research*. Washington DC, USA: The International Bank for Reconstruction and Development/The World Bank

***Katrin Weigmann is a freelance journalist in Oldenburg, Germany.***

EMBO *reports* (2013) **14,** 597–600; published online 14 June 2013; doi:10.1038/embor.2013.82