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How to achieve international action on falsified and substandard medicines

Substandard and falsified medicines kill patients, yet progress on the twin challenges of safeguarding the quality of genuine medicine and criminalising falsified ones has been held back by controversy over intellectual property rights and confusion over terms.

Amir Attaran and colleagues propose a global treaty to overcome the problems

Every day patients in need of effective treatment receive substandard or fake drugs and other medical products.^{1 2} At best patients taking these compromised products get no relief from their symptoms; at worst they may die. In poor countries, half of medicines for some deadly diseases are fake and have little or no active ingredient.³ In rich countries, medicine safety is better, but substandard and falsified drugs still cause thousands of adverse reactions and some deaths.⁴⁻⁶ As the outsourcing and international trading of medicines becomes standard, patients everywhere are vulnerable.^{4 5}

In 2010, after years of debate, WHO's member states established a working group to decide how best to tackle this scandal, but progress remains halting.⁷ The working group (now called the member state mechanism) still cannot agree how to define the various poor quality medicines, much less settle on any concrete actions.

There are several reasons for this inadequate progress, yet all are possible to overcome. In this article we—a diverse group of authors from the health professions, health charities, legal and medical academia, and former or current government officials in health—outline the current challenges and propose possible solutions.

Common interest

The most fundamental reason for current and past inaction is a failure to recognise shared goals. Although drug companies, non-governmental organisations, and governments all want reliable access to safe and effective medicines and deplore unsafe fake medicines, it is difficult to achieve agreement on action because discussions too often trespass into conflict prone areas such as pharmaceutical pricing or intellectual property.

For agreement to be achieved, care and restraint will be needed to avoid these distract-

ing arguments. One source of disagreement is that anticounterfeiting laws in some countries give prominence to the protection of commercial interests and pay little or no attention to protecting public health interests.⁸ In East Africa, poorly worded reforms to anticounterfeiting laws, supported by some pharmaceutical companies, threatened to impede the availability of generic medicines on which most ordinary Africans depend.^{9 10} Likewise in Europe, customs authorities seized legitimate generic AIDS and cancer medicines that were in transit from India to Brazil because they infringed European intellectual property and were ostensibly counterfeit.¹¹ Rather than promoting understanding and trust, these decisions generated an understandable activist backlash because they endangered affordable access to medicines.⁸ If progress is to be made, not only must such apparently provocative actions be avoided, but the rush to controversy must be tempered by all parties on all sides.

Clearer definitions

Such clashes are often caused by a second fundamental problem: the absence of a clear, internationally agreed terminology to define different sorts of legitimate or illegitimate medicines (box 1, see bmj.com).

Everyone agrees that there are two categories of legitimate medicine on the market: proprietary medicines, which are initially marketed under patent, and generic medicines, which are lawful copies of the proprietary medicines either because in a given country the patents have expired or were never granted or because the manufacturer has a licence to use the patent. Despite price differences, both proprietary and generic medicines are produced according to good manufacturing standards, are properly regulated for quality, and can bear brands or trademarks.

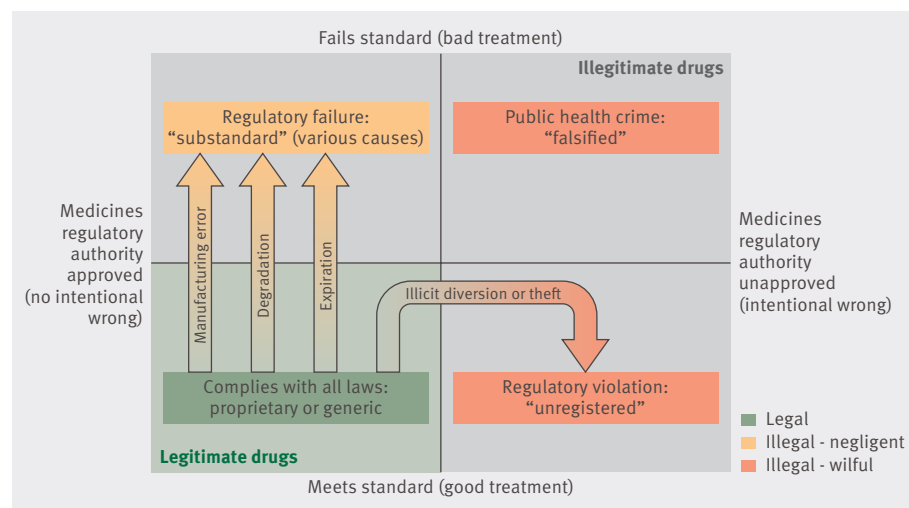


Fig 1 | Categories of legitimate and illegitimate medicine

The situation and the terminology are far messier for illegitimate medicines. In the past WHO distinguished between “substandard” and “counterfeit” medicines, but last year member states chose to lump them together in the new term “substandard/spurious/falsely-labelled/falsified/counterfeit medical products” (SSFFC).¹⁴ However, placing all illegitimate medicines under the SSFFC umbrella gives the misleading, mistaken impression that they are all deficient in the same way, when actually there are many possible deficiencies, each requiring different solutions. We therefore propose new definitions, which refine the views of WHO member states (fig 1).¹⁵

An important strength of the definitions that we propose is that they do not draw on any intellectual property questions or use the confusing word counterfeit. According to international intellectual property law, a “counterfeit” medicine is one that infringes a registered trademark by bearing an identical or near identical mark.¹⁶ Deliberate counterfeiting is a private economic wrong, which can occur separately from or together with the public health wrong of poor medicine quality. Thus it is a mistake (but a common one) to use the adjective “counterfeit” to refer to medicines that endanger public health. Accordingly we avoid the term here.

“Substandard” medicines are those that for unintentional reasons do not meet the legally required quality specifications of a country’s regulators (usually a specialised medicine regulatory authority). As noted elsewhere, substandard medicines have various deficiencies and causes—for example, the raw ingredients may be of poor quality, errors may occur in manufacturing, or mishandling may cause the medicine to degrade or expire.⁸ Each of these technical problems requires a different solution.

“Unregistered” medicines are those that do not have the legally required marketing authorisation of the country’s regulators to be imported or sold there—for example, internationally diverted or stolen medicines. Unregistered medicines can occur unintentionally, but more often illicit diversion or theft implies criminal intent to circumvent regulatory approval.

With both substandard and unregistered medicines, some aspect of the medicine does not meet the regulator’s legal requirements. Generally such products are also “falsely labelled” because they deviate from the regulator’s approved packaging (expired medicines, properly labelled with an end date, are the exception).

The final category is “falsified” medicines. Similar to substandard medicines, the falsified medicines are unlawful in violating the regulator’s quality specifications—but what truly defines and distinguishes them is criminal intent. Thus it takes more than a negligent breach of the

Box 2 | Examples of dangerously compromised medicines in 2011-12

Substandard heart medicine

More than 125 people died in Pakistan of bone marrow suppression after a public cardiology pharmacy provided generic isosorbide-5-mononitrate tablets adulterated with a toxic overdose of pyrimethamine, an antimalarial drug. The substandard product was the result of a manufacturing error, although police allege that company officials learnt of the error and sold the medicine anyway.²³ If the allegation proves true, the medicine would be reclassified as falsified.



Falsified antiretrovirals

In Kenya, Médecins Sans Frontières (MSF) unintentionally provided patients with falsified tablets of zidovudine, lamivudine, and nevirapine that criminals had inserted into its supply chain.²⁴ The falsified product mimicked the appearance of a generic antiretroviral, but tablets were “in varying degrees of deterioration, ie moulding, discolouration.”²⁵ Once the problem was discovered, MSF followed-up about 3000 patients with proper medicines and counselling.

Falsified cancer medicine

Authorities globally are combating falsified bevacizumab of unknown origin. The falsified product closely matches the appearance of the real medicine, but tests indicate that it contains starch and acetone instead of active ingredient.²⁶ The fakes were trafficked on a complex supply chain, through Turkey, Switzerland, and Denmark to US, in part by a Canadian firm and its offshore affiliates. The extent of harm to patients is unknown.

regulator’s legal requirements to make a medicine falsified; there must also be a deliberate intent to deceive or wilful blindness. For example, while an expired medicine is merely substandard, if the date is altered to make it appear not expired, that deliberate fraud makes it falsified. Lawyers call this element of criminal intent *mens rea* (guilty mind), and it signals to the justice system to prosecute and punish instances of falsified medicines as serious crimes, not just regulatory violations or civil negligence claims.

Surveillance and research

The third problem is that there is little reliable information on the global scale of the falsified medicine problem.¹ The UN Office of Drugs and

Crime implicates China and India as the major exporters of “counterfeit” medicines, some of which are doubtless also falsified, because both governments acknowledge problems enforcing medicine quality laws.¹⁷⁻¹⁹ Case reports and small scale studies document products containing the wrong ingredients or bogus ingredients such as chalk, with the deception disguised by sophisticated copies of the packaging and holograms, or the cunning use of wrong ingredients that mimic the proper active ingredient in analytical tests.^{3 20-22} These studies leave no doubt that falsified medicines harm and kill—sometimes hundreds of people at a time (box 2).

But how many incidents of falsified medicine are there, how are they trafficked, and most importantly, how can the public be better protected? More surveillance and research are needed to answer these questions satisfactorily. WHO has estimated that less than 1% of medicines in developed countries, rising to over 10% in developing countries may be “counterfeit” (using its overbroad definition of the term).²⁷ Although an underestimate, in 2009 the Pharmaceutical Security Institute (an organisation set up by 24 drug companies in the 1990s) detected about 2000 incidents of illegitimate medicines of all kinds—five a day—in 118 countries and affecting 808 products in nearly all therapeutic categories.²⁸ In the European Union, medicines are now the leading illegitimate product seized at the border, increasing 700% from 2010 to 2011 (and the seizures would be even higher, if the EU enforced more than just intellectual property violations).²⁹

The pharmaceutical industry, researchers, and governments must better partner in acquiring, analysing and publicising knowledge. The Pharmaceutical Security Institute maintains a large database on various medicine crimes, but the industry keeps nearly all the data secret, lest transparency should undermine law enforcement efforts and deter patients from consuming its products. Unfortunately, the industry’s secrecy deprives researchers and governments of data that would help raise public awareness of falsification, catalyse political action, and thus improve patient safety. Some form of cooperation and compromise must be reached, whereby secrecy is protected during police investigations but biomedical and criminological researchers gain access soon after.⁷ Just as clinical trial registries have begun to make the industry’s once secret trial data more available, more transparency of the industry’s medicine crime data is possible.

Avoid conflating issues

The fourth problem is the mistaken tendency to conflate quality of medicines with tangential concerns such as intellectual property rights.³⁰ The confusion arises because pharmaceutical

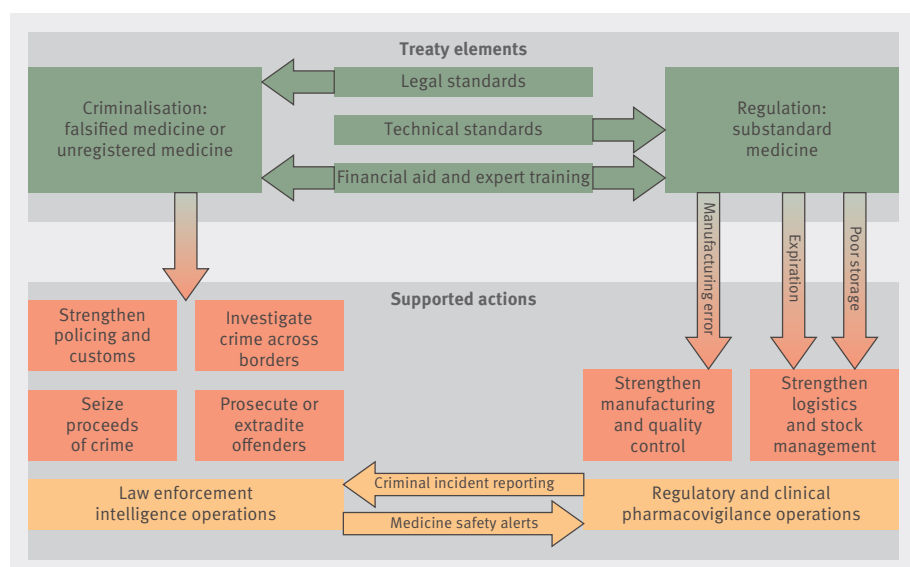


Fig 2 | Elements of a treaty to improve the safety of medicines. The figure shows the linkages between treaty elements (green), directly supported actions (red), and supporting information exchanges (orange)

companies sometimes enforce their intellectual property to force counterfeited copies of their products off the market, some of which may also be falsified. (This is why we recommend reserving the term “counterfeit” for private trademark violations and “falsified” for public health crimes.)

Arguments by some non-governmental organisations that “the high price of pharmaceuticals” causes falsification or that lower prices would “eliminate the incentive for the business” are also based on mistaken conflation.^{31 32} Such arguments fail to recognise that any legitimate medicine, regardless of price, can be produced more cheaply and profitably by criminals using fake instead of real ingredients. Thus falsification occurs not just in expensive proprietary medicines but also the cheapest generic medicines, including those on the WHO model list of essential medicines that cost only pennies (for example, ampicillin, chloroquine, or tetracycline).^{33 34} Worryingly, medicines on WHO’s essential list may be especially attractive to falsify because there is a huge global demand and because most are unpatented, meaning criminals face no risk from angry patent holders suing or demanding prosecution. Even basic generics can be falsified with tragic results—for example falsified paracetamol syrup has killed hundreds (mostly children) in Bangladesh, Haiti, India, and elsewhere.³⁵ Like most crime, falsification is opportunistic, occurring where regulatory defences are lowest, not necessarily where profits are highest.

Using international law

We argue that tackling the challenges of poor quality, unsafe medicines requires a comprehensive global strategy on which all stakeholders

agree. Both falsified and substandard medicines endanger public health, but their countermeasures are different.⁸ A new global treaty could tackle them simultaneously and synergistically through legal, technical, and financial measures (fig 2).

The governance of the global medicine trade currently suffers from a dangerous imbalance: international trade laws force open countries’ markets to imported medicines and pharmaceutical ingredients, but no complementary international health laws defend countries from trafficked products of dangerously bad quality. Purely technical initiatives are not sufficient to safeguard quality because they are not legally binding (box 3, see bmj.com). A binding international law on drug quality—that is, a treaty—is needed to complement the existing trade treaties and put public health on an equal plane.

Currently, the biggest problem with the governance of falsified medicines is that they are legal in global trade.⁴⁰ Responsible governments can and do prohibit falsified medicines under national law but remain vulnerable to organised criminals doing business in “haven” countries (both rich and poor) where laws or enforcement are lax—30% of countries have little or no medicine regulation according to WHO. In other contexts global treaties have helped governments strengthen their laws and cooperate internationally to clamp down on the havens—for example, on human trafficking or money laundering. The lack of a treaty means there is generally no agreement on which medicines are wrongful or criminal; no requirement for police to cooperate across borders in carrying out international investigations; and no requirement for prosecutors to share evidence or to respond to extradition requests to

bring perpetrators to justice.⁴⁰ These omissions translate into impunity for medicine criminals.

A successful treaty would deal with both falsified and substandard medicines but treat them differently. Using our definitions, falsified medicines are deliberate, intentional frauds and should be prohibited using criminal measures. In contrast, substandard medicines are unintentional or negligent errors that require regulatory measures to correct. The “positive” regulatory agenda and the “negative” criminal agenda are synergistic, as in other policy contexts (for example, food is regulated for safety, but adulterating food is a crime). Both agendas depend primarily on national medicine regulatory authorities, with ancillary support from customs, police, justice ministries, and frontline healthcare workers. As well as setting norms and expectations for governments, a treaty could raise new money through a dedicated financial mechanism to help needy countries build regulatory capacity for medicines, assuring quality manufacturing and training healthcare workers.

Thus the growing political energy to fight falsified medicines could, if wisely channelled into a treaty that also includes substandard medicines, provide new financing and reinforced capabilities against both dangers.

Action plan towards a global treaty

The treaty would need to fulfil five functions:

- Define legally the different types of illegitimate medicines, possibly using the terms we propose, so as to avoid confusion and unwelcome over-reaches against legitimate medicines
- Define new public health crimes in international law, such as to manufacture, traffic, or sell falsified medicines
- Mandate intergovernmental cooperation so that countries report, investigate, and prosecute transborder crimes and seize criminals’ assets
- Create an ongoing intergovernmental forum to protect the legitimate medicines trade, such as by setting global standards for authenticating medicines with tracking and tracing technologies or by setting standards for medicine sales on the internet
- Include administrative provisions, particularly to give financial and technical assistance to strengthen medicine regulatory authorities in poorer countries.

Other consensus building exercises have identified many of the same elements,⁴¹ and conveniently, these elements have precedents in other treaties. A 1929 treaty to criminalise counterfeit banknotes internationally provides an obvious analogy for falsified medicine.⁴² This month a new protocol under today’s leading public health

treaty, the Framework Convention on Tobacco Control (FCTC) will legally mandate global tracking and tracing for tobacco products and internationally criminalise illicit trade—oddly making the law tougher on cigarette falsification than on medicine falsification. The FCTC also shows that treaties can raise new financial resources: nearly \$250m (£155m; €190m) is now spent annually on global tobacco control.⁴³ More dramatic examples exist in various environmental treaties, through which the Global Environment Facility has raised over \$50bn in foreign aid directly and in co-funding.⁴⁴ These and other successful precedents are adaptable for medicines.

What are the reasonable next steps? WHO's member states should ask WHO staff to embark on a similar process to that which created the FCTC, which began with a technical working group and led to formal negotiations among diplomats in an international negotiating body. That project should have the limits we describe here, such as excluding work related to intellectual property, and should involve other international organisations when matters exceed WHO's public health mandate (for example, the UN Office on Drugs and Crime is better suited to law enforcement than WHO). To build the political case and will for action, the pharmaceutical industry and Pharmaceutical Security Institute should cooperate with independent researchers on studies that generate knowledge and raise awareness about the scale and provenance of illegitimate medicines. This starting framework, we believe, avoids unnecessary controversy and can better enable governments, companies, advocates, and the health professions to protect the public's health.

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Neglected tropical diseases
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In resource poor countries, substandard medicines are predictably the result of structural negligence or poor manufacturing practices

COMMENTARY

Substandard medicines are the priority for neglected tropical diseases

Attaran and colleagues propose new definitions for the quality of medicines and plead for a global treaty tackling both substandard production and falsification.¹ We support this, as the international community tends to concentrate its efforts on falsified medicines, whereas substandard drugs are just as much a threat.² Moreover, in practice the distinction can be difficult.

We recently described the case of a poor quality medicine from Bangladesh that did not contain its active ingredient, miltefosine.³⁻⁴ The medicine, authorised by the national regulatory authorities, was manufactured locally for the Bangladeshi elimination programme for visceral leishmaniasis, a neglected tropical disease. The problem surfaced only after reports of abnormally high numbers of treatment failure.

According to the proposed definitions, this medicine is substandard. Whether it is falsified remains unclear. Attaran et al argue that a criminal intent would make the manufacturing worth a more serious punishment. We disagree with this approach, not only because it is often impossible to discern a manufacturer's intent but also because the effect of poor quality medicines on public and individual health should be the prime concern. The substandard miltefosine may have been the result of a lack of resources, negligence, or fraud, but the outcome is the same: unnecessary and preventable morbidity and mortality. In resource poor countries, substandard medicines are predictably the result of structural negligence or poor manufacturing practices.⁵ Structural negligence in pharmaceutical production should never be considered less important than a deliberate or fraudulent action because the consequences are equally serious for the final user.

Prioritising prevention

Although a global treaty will provide a welcome legal framework, we want to see problems with medicine quality anticipated rather than dealt with afterwards. The lack of resources of many regulatory authorities prevents them from enforcing standards on manufacturers and distributors. The World Health Organization should help strengthen regulation in resource limited coun-

tries. In the public sector appropriate tender procedures should be developed, with adequate quality criteria for manufacturers and products, and well defined procurement policies.⁶ These procedures should be public, to maximise transparency and accountability towards citizens.

Disproportionally affecting neglected tropical diseases

Traditionally, medicine quality has been ignored in neglected tropical diseases, though scattered reports show that serious problems exist. For visceral leishmaniasis at least three other incidents with poor quality medicines have been described, from India, Nepal, and Sudan.⁷⁻⁹ All came to light only because of abnormally high failure rates or life threatening toxicities, though the poor manufacturing practices could have been detected in advance by regulatory inspections. Attaran and colleagues point out that falsification is opportunistic and often occurs with cheap generics. Likewise, the lack of financial incentives in the market for medicines for neglected tropical diseases does not protect these medicines from illegitimacy. Public sector tenders predictably result in purchases from the cheapest possible supplier, with no regard for quality specifications. Patients with these neglected diseases may therefore be disproportionately at risk from substandard medicines.

Internationally, guidance should be provided for the quality assurance of medicines for neglected tropical diseases. The WHO prequalification programme provides such guidance based on structural preventive measures, but it is currently limited to HIV/AIDS, malaria, tuberculosis, and reproductive health. This year, an important first step was made when the programme invited manufacturers to submit two antihelminthic drugs for evaluation, but expansion is needed. Quality assurance is further complicated by a lack of monographs for medicines for neglected diseases in the major international pharmacopoeias, though the United States Pharmacopeia has recently opened an online section to make quality standards for medicines approved in any country publicly available (www.usp-mc.org/).

The focus of concerted actions should be on the effect of poor quality medicines as a whole and should tackle structural substandard production. A patient centred, integrated approach to protecting neglected patients from all dangerous medicines cannot be further postponed.

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