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Substandard drugs: a potential crisis for public health

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Poor-quality medicines present a serious public health problem, particularly in emerging economies and developing countries, and may have a significant impact on the national clinical and economic burden. Attention has largely focused on the increasing availability of deliberately falsified drugs, but substandard medicines are also reaching patients because of poor manufacturing and quality-control practices in the production of genuine drugs (either branded or generic). Substandard medicines are widespread and represent a threat to health because they can inadvertently lead to healthcare failures, such as antibiotic resistance and the spread of disease within a community, as well as death or additional illness in individuals. This article reviews the different aspects of substandard drug formulation that can occur (for example, pharmacological variability between drug batches or between generic and originator drugs, incorrect drug quantity and presence of impurities). The possible means of addressing substandard manufacturing practices are also discussed. A concerted effort is required on the part of governments, drug manufacturers, charities and healthcare providers to ensure that only drugs of acceptable quality reach the patient.

Introduction

Poor-quality medicines can reach the market through substandard production of legitimate drugs due to inadequate quality-control processes during manufacture, as well as by deliberately fraudulent practices. The relative contribution of the two sources is unknown; however, genuine but low-quality drugs are likely to account for the majority of cases [1]. To date, legislation has focused on the control of deliberately falsified drugs, but poor-quality legitimate drugs, i.e. those that have gone through some sort of regulatory procedure, are more commonly seen and pose a greater threat to patient health, so both issues need to be tackled. In recent years, there have been a number of high-profile recalls; for example, the European Medicines Agency (EMA) recommended the recall of eight generic clopidogrel-containing medicines for which the active pharmaceutical ingredient (API) was produced in India, following an inspection of the manufacturing site [2], and in the USA all products compounded at New England Compounding Pharmacy's facility in Framingham, Massachusetts were recalled following a

fatal outbreak of fungal meningitis associated with injectable steroids [3]. In some cases, there have been import bans on drugs from companies suspected of having substandard production practices (e.g. Ranbaxy [4, 5]). However, more must be done to improve the manufacturing practices and registration of drugs, so that poor-quality drugs (albeit approved by a regulatory authority) do not reach the market.

In this article, we aim to raise awareness of the problem of substandard drugs; a problem that we regard as having the potential to be a public-health crisis. We highlight the types of formulation defects that can occur and the consequences of substandard drugs. We also review some of the efforts being made to ensure that manufacturing and quality-control processes comply with internationally accepted practices.

Definitions

In 2009, the World Health Organization (WHO) defined 'substandard' drugs (also called 'out of specification products') as 'genuine medicines produced by manufacturers authorized by the NMRA [national medicines regulatory

authority] which do not meet quality specifications set for them by national standards' [6]. A new definition was proposed by the WHO in May 2010 [7]: 'Each pharmaceutical product that a manufacturer produces has to comply with quality standards and specifications at release and throughout the product shelf-life required by the territory of use. Normally, these standards and specifications are reviewed, assessed and approved by the applicable NMRA before the product is authorized for marketing. Substandard medicines are pharmaceutical products that do not meet their quality standards and specifications.'

The WHO defines 'counterfeit' drugs as 'medicines that are deliberately and fraudulently mislabelled with respect to identity and/or source' [8]. It also states that both branded and generic products may be counterfeited and that 'counterfeit medicines may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient or too much active ingredient, or with fake packaging'. However, because of the potential misunderstanding of the term 'counterfeit' – which, in the context of intellectual property, refers specifically to trademark infringement – the phrase 'falsified medicines' is used by some authorities, particularly in Europe. The Commission of the European Communities defines these as 'medicinal products which are falsified in relation to their identity, history or source. These products . . . usually contain sub-standard or false ingredients, or no ingredients or ingredients in the wrong dosage, including active ingredients' [9].

Thus, falsified drugs are highly likely to be of substandard quality, possibly containing no API. However, only a small proportion of substandard drugs are falsified; the rest reach the market as a result of poor manufacturing practices, inadequate quality-control processes, incorrect storage or inappropriate packaging, or a combination of these factors. This can affect both branded and generic drugs. In many cases, the reason why a drug product is substandard (i.e. deliberate falsification or poor manufacturing practice) is not stated or is not known. Whether or not a drug product is substandard because of criminal intent or because of failures in manufacturing, storage, etc. is immaterial to the patient because the impact on their health will be the same, regardless of cause [10]. In this article, we consider the term 'substandard' to apply both to legally approved but poor-quality drugs and to falsified drugs, but we focus on the former with regard to reviewing potential solutions.

The terms 'medicine', 'medications' and 'drugs' are used interchangeably in this article.

Literature search

This narrative review was based on literature searches conducted using PubMed to identify English-language articles giving relevant examples of substandard drugs; identified

articles were hand searched for further relevant examples. A systematic review of all publications was not intended and thus a search for published literature using PubMed alone was deemed to be adequate. Search terms included combinations of the following: substandard, quality, resistance, (drug OR drugs OR medication OR medications OR medicine OR medicines), (impurity OR impurities OR contamination OR contaminant OR contaminants). Searches were generally limited to recent publications (since 2000). Data from publications were included and tabulated if they provided examples of the marketing of substandard drugs, based on analytical or clinical evidence. Internet searches using similar terms were also performed using the Internet search engine Google, and specific searches were conducted of relevant websites [e.g. the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) websites].

Using examples identified through this search, the article will review information on substandard medicines, including the following: inappropriate API content, impurities and inconsistent pharmacological response due to variable drug content; the prevalence of and potential adverse health effects associated with use of substandard drugs; and methods by which drug quality might be improved.

Defective drug formulation

In cases of substandard medication that arise through inadequate production processes, rather than through deliberate falsification of drugs, the lack of quality may be the result of a variety of factors, including the following: inadvertent use of substandard or incorrect APIs or excipients; poor control of drug quantity; manufacturing processes that cause contamination or do not adequately ensure sterility; and inadequate packaging design or quality. In addition, ineffective quality-control measures, either on the part of the manufacturer or the NMRA, allow such faults to remain undetected.

Drug content

Any formulation of a medication may be regarded as substandard if it has either too much or too little of the API compared with the formulation specifications. Official national pharmacopoeias, such as the British Pharmacopoeia (BP) and United States Pharmacopoeia (USP), publish the quality standards for medicinal substances and preparations manufactured or sold in the country. The information given specifies the acceptable limits for the amount of the API that should be present in a given formulation. However, many examples from a range of drug classes have been published of over/underconcentration of APIs in marketed drugs (see Table 1 [11–39]). In some cases, all sampled antibiotics or antimalarials were found to contain API concentrations outside the officially specified limits [11].

Table 1

Substandard drugs: drug content

Drug(s)	Issue	Region/countries	Reference
Antimalarials			
Chloroquine phosphate, chloroquine sulphate and quinine sulphate	Chloroquine phosphate: 70% of capsules (<i>n</i> = 29), 100% of syrup samples (<i>n</i> = 20) and 94% of tablets (<i>n</i> = 18) outside BP limits. Chloroquine sulphate: 79% of tablet samples (<i>n</i> = 19) and 73% of syrup samples (<i>n</i> = 20) outside BP limits Quinine sulphate: 24% of tablet samples (<i>n</i> = 17) outside BP limits	Nigeria	Taylor <i>et al.</i> (2001) [11]
Amodiaquine and sulfadoxine-pyrimethamine	11% of sulfadoxine samples (<i>n</i> = 18) failed the test for content of APIs	Tanzania	Minzi <i>et al.</i> (2003) [12]
Ceftriaxone	9% of generics (<i>n</i> = 35) failed to achieve minimum 97% content specified in EP	Brazil, Pakistan and Philippines	Lambert and Conway (2003) [13]
Chloroquine, quinine and antifolates	Drugs purchased from unofficial vendors: 38% of chloroquine (<i>n</i> = 133), 74% of quinine (<i>n</i> = 70) and 12% (<i>n</i> = 81) of antifolate samples had no API or insufficient, incorrect or unknown ingredients Tablets collected from patients who self-medicated before consultation: of 15 quinine or chloroquine samples collected, six (40%) contained no API, one had an insufficient dose and two contained quinine instead of chloroquine	Cameroon	Basco (2004) [14]
Artesunate	53% of samples (<i>n</i> = 188) contained no artesunate	Burma, Lao People's Democratic Republic, Vietnam, Cambodia and Thailand	Dondorp <i>et al.</i> (2004) [15]
Chloroquine phosphate tablets and chloroquine syrup	6.7% of syrup samples (<i>n</i> = 25) and 20% of tablets (<i>n</i> = 25) failed to meet content specifications	Yemen	Abdo-Rabbo <i>et al.</i> (2005) [16]
Sulfadoxine-pyrimethamine and amodiaquine	45.3% of sulfadoxine-pyrimethamine and 33.0% of amodiaquine samples (<i>n</i> = 116) were substandard; 40.5% of samples did not meet USP specifications for content and/or dissolution	Kenya	Amin <i>et al.</i> (2005) [17]
Artemisinin-derivatives: artemether, arteether, artesunate or DHA	Seven of 24 samples were underdosed and two of two samples were overdosed (i.e. outside of allowed range of 95–105%) according to European requirements DHA was the API in 57% of the underdosed samples	Kenya and Democratic Republic of the Congo	Atemnkeng <i>et al.</i> (2007) [18]
Sulfadoxine-pyrimethamine, amodiaquine, mefloquine, artesunate, artemether, DHA and artemether-lumefantrine fixed-dose combination	35% of samples (<i>n</i> = 210) failed tests for the concentration of APIs compared with internationally accepted standards	Africa	Bate <i>et al.</i> (2008) [19]
Chloroquine, sulfadoxine-pyrimethamine, quinine, amodiaquine, artesunate and artemether-lumefantrine	Nine of 77 (12%) samples had substandard concentrations of API	Burkina Faso	Tipke <i>et al.</i> (2008) [20]
Artesunate, DHA, sulfadoxine-pyrimethamine, quinine and chloroquine	37% of the samples tested (<i>n</i> = 225) did not meet USP limits for the amount of API 46% of quinine samples and 39% of sulfadoxine-pyrimethamine samples did not meet the criteria	Nigeria	Onwujekwe <i>et al.</i> (2009) [21]
Artemisinin-based drugs	Thirteen of 14 (93%) contained either too low or too high a dose of the specified drug	Ghana	El Duah and Ofori-Kwakye (2012) [22]
Antituberculosis drugs			
Isoniazid and rifampicin	10% (<i>n</i> = 40) of samples contained <85% of stated content 21% of fixed-dose combinations were substandard vs. 13% of single-drug samples	Colombia, Estonia, India, Latvia, Russia and Vietnam	Laserson <i>et al.</i> (2001) [23]
Isoniazid and rifampicin	Isoniazid: 100% of tablet samples (<i>n</i> = 4) were outside BP limits Rifampicin: 33% of capsule samples (<i>n</i> = 15) were outside BP limits	Nigeria	Taylor <i>et al.</i> (2001) [11]
Other antibiotics			
Amoxicillin, ampicillin, ketoconazole and metronidazole	Amoxicillin: 25% of capsule formulations (<i>n</i> = 32) and 40% of dry syrup formulations (<i>n</i> = 5) were outside BP limits Ampicillin: 59% of capsules (<i>n</i> = 39) and 71% of dry syrup formulations (<i>n</i> = 7) were outside BP limits Ketoconazole: 80% of cream preparations (<i>n</i> = 5) were outside BP limits Metronidazole: 100% of suspension formulations (<i>n</i> = 5) and 72% of tablets (<i>n</i> = 36) were outside BP limits	Nigeria	Taylor <i>et al.</i> (2001) [11]

Table 1

Continued

Drug(s)	Issue	Region/countries	Reference
Benzathine benzylpenicillin, ceftriaxone, chlortetracycline, ciprofloxacin, clotrimazole, co-trimoxazole, doxycycline and erythromycin	33% of 21 products for STDs did not contain the stated dose of API The highest deficit was 48% (co-trimoxazole and benzylpenicillin)	Burma	Prazuck <i>et al.</i> (2002) [24]
Ampicillin, tetracycline and chloroquine. Acetylsalicylic acid also included in study	The proportion of substandard drugs decreased significantly from 46% ($n = 366$) to 22% ($n = 300$) between 1997 and 1999 ($P < 0.001$) 4% of drugs had too little or too much API; 1% had no API (1999 data)	Lao People's Democratic Republic	Syhakhang <i>et al.</i> (2004) [25]
Clarithromycin	9% ($n = 65$) of samples did not contain 95–105% of the dose of API specified in the label of the reference (manufactured by Abbott)	Multinational (18 countries)	Nightingale (2005) [26]
Ciprofloxacin	17% of samples from Latin America did not meet criteria for content Six of 30 samples of generic eye drops had <95% of the stated drug content (range –36 to –16%); 24 of 30 had >105% of stated content (37% had >120%)	India	Weir <i>et al.</i> (2005) [27]
Ciprofloxacin	Three of 16 samples of generic tablets had 90–95% and one of 16 had >105% of the dose of API stated in the label	Multinational	Trefi <i>et al.</i> (2007) [28]
Amoxicillin	56% ($n = 72$) of capsules and 8% ($n = 39$) of suspensions had API levels outside of pharmacopoeial limits 38% of all samples ($n = 111$) had API levels outside of pharmacopoeial limits after storage for 38 days	Lebanon, Jordan, Egypt and Saudi Arabia	Kyriacos <i>et al.</i> (2008) [29]
Antibiotics (ciprofloxacin, erythromycin), antimalarials (chloroquine) and antimycobacterials (isoniazid, rifampicin)	12% ($n = 281$) of samples from Delhi failed tests for the concentration of APIs compared with internationally acceptable standards	India	Bate <i>et al.</i> (2009) [30]
Amoxicillin, chloramphenicol, tetracycline, co-trimoxazole and ciprofloxacin	18% ($n = 104$) of samples had small deviations in the dose of API (less than BP standards)	Indonesia	Hadi <i>et al.</i> (2010) [31]
Amoxicillin, ampicillin and cephalixin	10% (19 of 185) failed quantitative tests according to USP 30	Purchased in Cambodia (31% domestically manufactured)	Okumura <i>et al.</i> (2010) [32]
Immunosuppressants Tacrolimus	The standard deviation of content for the generic versions of Prograf Tenacrine, Tacrobell and T-Inmun (up to 30 of each) was 29.3, 6.9 and 5.6, respectively	Mexico	Petan <i>et al.</i> (2008) [33]
Cardiovascular Streptokinase	Thirteen of 16 products exhibited only 20.8–86.6% of the activity stated in the label	Multinational	Hermentin <i>et al.</i> (2005) [34]
Carvedilol	48.6% ($n = 35$) of generic samples failed to meet EP and Roche specifications for content (95–105%)	Multinational (19 countries)	Smith <i>et al.</i> (2006) [35]
Antihypertensives	20% ($n = 10$) of drugs tested were substandard in terms of API content at time of purchase 70% were substandard after 6 months in accelerated storage conditions	Rwanda	Twagirumukiza <i>et al.</i> (2009) [36]
Ramipril	24% ($n = 17$) of generic copies of Tritace failed to meet Sanofi-Aventis specifications (90–105% of label claim) for the amount of API This increased to 47% after storage for 3 months	Italy	Angeli and Trezza (2009) [37]
Oncology Docetaxel	Twenty-one of 31 commercially available generic versions of Taxotere had <90% of expected mass of docetaxel, and 11 of these contained <80% of expected mass	Multinational (14 countries in Asia, Africa, the Middle East and Latin America)	Vial <i>et al.</i> (2008) [38]
Dermatology Isotretinoin (acne)	Four of 14 generics failed tests for content following accelerated shelf-life tests, based on Roche criteria for content Two of 14 samples and three of 14 samples failed tests for content according to EP and USP specifications, respectively	Not specified	Taylor and Keenan (2006) [39]

Abbreviations are as follows: API, active pharmaceutical ingredient; BP, British Pharmacopoeia; DHA, dihydroartemisinin; EP, European Pharmacopoeia; STD, sexually transmitted disease; USP, United States Pharmacopoeia.

Inappropriate packaging can affect formulation content in certain storage conditions. For example, a study of generic versions of ramipril tablets found that, on initial inspection, four of 17 samples (24%) did not meet the label specifications for drug content. After 3 months of storage in temperature-stressed conditions (40°C and 75% relative humidity), a further four samples (total 47%) failed to meet the content specifications [37].

In some cases, a product may contain no API or the drug content may be completely different to that stated on the label. This may occur through deliberate falsification, but as the examples shown below demonstrate, accidental mislabelling may also occur.

- One batch of the antibiotic Rofact® (rifampicin) was mislabelled; bottles actually contained the anti-epileptic clonazepam (Canada, May 2009) [40].
- One lot of minocycline was mislabelled as amlodipine (Canada, March 2011) [41].
- One lot of bottles containing finasteride was labelled as containing citalopram (USA, March 2011) [42].
- Zopiclone was substituted for furosemide in a possible packaging mix-up (France, June 2013) [43].

Impurities

An impurity may be defined as any substance in the product that is neither the chemical entity defined as the drug nor an excipient [44]. Impurity profiling is required as part of the registration process by many regulatory authorities, including the FDA and the European Union's Committee for Medicinal Products for Human Use (CHMP). Impurities fall into one of three categories – organic substances, inorganic substances and residual solvents [45] – and may include starting materials, intermediate compounds, reagents and catalysts, heavy metals, degradation products, polymorphic forms (alternative crystal forms with potentially different dissolution profiles) and enantiomeric impurities, as well as extraneous contaminants. Impurities can arise in formulations due to poor manufacturing procedures and storage conditions (Table 2 [13, 23, 26, 28, 34, 35, 37–39, 46–59]). Impurities can alter medication properties or be toxic. Probably the best known cases of contamination involve diethylene glycol (DEG); at least 14 mass poisonings have been documented that were due to the presence of DEG in pharmaceutical preparations [47, 48]. Indeed, it was an incidence of mass poisoning with DEG (in this case, due to the use of DEG as a diluent for a liquid preparation of sulfanilamide) that brought about the 1938 Federal Food, Drug and Cosmetic Act in the USA and created the regulatory role of the FDA [60].

Many cases of DEG poisoning are likely to have occurred as a result of DEG being substituted for the commonly used diluents propylene glycol or glycerine [47]. The substitution was probably deliberate at the level of

provision of an ingredient, although it is possible that contamination could have occurred during the manufacture of glycerine [47]. Subsequent use of the contaminated ingredient may not have been deliberate. However, whatever the cause of contamination of the raw materials, the responsibility for the safety of the drug product rests with the drug manufacturer, and appropriate testing of materials should be in place to prevent such occurrences.

In many other cases, contamination has clearly occurred due to poor manufacturing and/or quality-control processes, or unsuitable packaging. Contaminants have included the following: particulate matter in injectable cefotaxime [50]; small glass particles in bottles of generic atorvastatin tablets [61]; degradation products in docetaxel, streptokinase and clopidogrel [34, 38, 56]; and potentially genotoxic impurities in batches of nelfinavir due to incomplete removal of ethanol following the cleaning of manufacturing equipment [54]. In 1990, unacceptably high levels of benzene were detected in bottled Perrier water [62], which highlighted the need to understand the impact of ingredient interactions and packaging. The presence of benzene was thought to arise from the reaction of the preservative benzoic acid with ascorbic acid, possibly accelerated by the presence of citric acid, heat and light [63, 64]. In other cases, bacterial contamination in several different drug products has been attributed to unhygienic practices [46].

In addition to the official recall notices and studies published in peer-reviewed journals, there are numerous examples in the press of contamination in marketed drugs, such as the incidents described below.

- Albusax (a paclitaxel formulation produced in India) was found to contain excessive endotoxin levels and was withdrawn from the market (April 2009) [65].
- Batches of Tylenol, Motrin, Roloids and Benadryl were recalled in the USA due to the presence of 2,4,6-tribromoanisole (January 2010) [66].
- Generic formulations of clopidogrel marketed in India and Europe were found to contain methyl chloride, which can cause hepatic, renal and nervous system damage [67].
- Methylidopa (Dopamet) 250 mg tablets produced in Cyprus were banned by the Tanzania Food and Drugs Authority. It was found that drug identification labels could be detached easily from the packaging, and there was 'vivid fungal growth' on the tablets (January 2011) [68].

Pharmacological variability and stability

Generic drugs can aid the provision of healthcare to a wide patient population, particularly in developing countries. However, generic formulations should only be marketed if their quality is equivalent to that of the originator drug. At present, to gain marketing approval, a generic drug only

Table 2

Substandard drugs: contamination

Drug(s)	Contaminant	Source (if known)	Countries	Reference
Miscellaneous				
Ampicillin, tetracycline, paracetamol, chloroquine and metronidazole	Bacteria Ampicillin: <i>S. aureus</i> in six of 16 Tetracycline: <i>B. subtilis</i> in five of 15, <i>P. Mirabilis</i> in 5 of 15 Paracetamol: <i>S. aureus</i> in five of 15, <i>A. aerogenes</i> in four of 15, <i>P. mirabilis</i> in three of 15 Choloquine: <i>B. subtilis</i> in 11 of 23, <i>A. aerogenes</i> in three of 23 Metronidazole: <i>B. subtilis</i> in three of 15, <i>S. aureus</i> in 13 of 15	The authors concluded the source to be unhygienic manufacturing practices and poor adherence to good manufacturing practice	Nigeria, USA and Panama	Itah <i>et al.</i> (2004) [46]
Paracetamol, cough expectorant, propolis, teething syrup, armillarisin, sulfanilamide, sedatives and silver sulfadiazine	Diethylene glycol	Contaminated propylene glycol or other glycols	Nigeria, USA, Panama, South Africa, India, Spain, Bangladesh, Argentina, Haiti and China	Schier <i>et al.</i> (2009) [47]; Schep <i>et al.</i> (2009) [48]
Orlistat	Nine of nine generic products contained higher levels of impurities than permitted by branded drug specifications	Side-chain homologues and unidentified impurities	India, Malaysia, Argentina, Philippines, Uruguay and Taiwan	Taylor <i>et al.</i> (2010) [49]
Antibiotics				
Cefotaxime	Particulate matter present in injectable antibiotics Injection of particles from two of three generic formulations into hamsters reduced capillary perfusion in muscle previously exposed to ischaemia and reperfusion		Germany	Lehr <i>et al.</i> (2002) [50]
Ceftriaxone	12% of generic formulations (<i>n</i> = 35) were not sterile; 15% contained impurities; 97% contained thiotriazinone (drug degradation product)		Brazil, India, Pakistan and Philippines	Lambert and Conway (2003) [13]
Clarithromycin	19% (<i>n</i> = 65) of generics did not meet Abbott criteria for ≤3% impurities		Multinational (18 countries)	Nightingale (2005) [26]
Ciprofloxacin	None of 16 generic samples analysed met the European Pharmacopoeia limits for levels of impurities. Samples contained fluorinated and nonfluorinated impurities		Multinational	Trefi <i>et al.</i> (2007) [28]
Anticoagulants				
Heparin	Oversulphated chondroitin sulphate	Contaminant not removed in production process	USA, Germany	Blossom <i>et al.</i> (2008) [51]
Heparin	<i>Serratia marcescens</i>	Prefilled syringes; the manufacturer was found to have inadequate controls to ensure sterility	USA	Blossom <i>et al.</i> (2009) [52]
Antituberculosis drugs				
Isoniazid and rifampicin	Two of 40 samples contained an additional unidentified chemical component		Colombia, Estonia, India, Latvia, Russia and Vietnam	Laserson <i>et al.</i> (2001) [23]
Oncology				
Docetaxel	Twenty-three of 31 generic formulations of Taxotere had an impurity content >3% Thirty-three unknown impurities were present at >0.05% in 31 generic versions of Taxotere	Included 7-epidocetaxel, a product of docetaxel degradation; others unidentified	Multinational (14 countries in Asia, Africa, the Middle East and Latin America)	Vial <i>et al.</i> (2008) [38]
Ophthalmology				
Endosol (balanced salt solution)	Endotoxin was present at concentrations exceeding the specified limit in 35% of samples Resulted in toxic anterior segment syndrome		USA	Kutty <i>et al.</i> (2008) [53]
Protease inhibitors				
Nelfinavir mesylate	Elevated levels of ethyl methanesulphonate	Ethanol cleaning of manufacturing equipment	Global	Pozniak <i>et al.</i> (2009) [54]

Table 2

Continued

Drug(s)	Contaminant	Source (if known)	Countries	Reference
Antidiabetics Glimepiride	In stressed conditions (storage at 60°C for up to 21 days), levels of glimepiride degradation products were higher vs. the reference (Amaryl) in two of 23 generic samples on day 7 and four of 24 samples on day 21 Other impurities and solvents were above reference specifications ($\leq 1\%$) in two samples		Italy	Attorse and Massi-Benedetti (2007) [55]
Cardiovascular Clopidogrel	>60% of 18 generics studied contained >4 times the amount of hydrolysis products or the <i>R</i> -enantiomer compared with Plavix After storage for 3 months at 40°C and 75% humidity, the differences were more pronounced	Degradation	Multinational (five countries)	Gomez <i>et al.</i> (2004) [56]
Streptokinase	Biochemical analysis by electrophoresis revealed additional bands on SDS-PAGE gels, suggesting impurities	Degradation suspected	Multinational	Hermentin <i>et al.</i> (2005) [34]
Carvedilol	Three of 35 samples of generics had excessive impurities (>3%) according to European Pharmacopoeia and Roche specifications	Not specified in abstracts	Multinational (19 countries)	Smith <i>et al.</i> (2006) [35]
Ramipril	32% ($n = 22$) of samples had impurities above the reference specifications ($\leq 5\%$) This increased to 68% after storage for 3 months	Determined as major metabolite	Italy	Angeli and Trezza (2009) [37]
Isosorbide-5-mononitrate	Antimalarial agent pyrimethamine	Manufacturing error: pyrimethamine added instead of pregelatinized starch	Pakistan	Attaran <i>et al.</i> (2012) [57]; Choudary (2012) [58]; World Health Organization (2012) [59]
Dermatology Isotretinoin (acne)	Eight of 14 generic samples failed criteria for total impurities Six of 14 samples contained five or more unknown impurities	Not specified	Not specified	Taylor and Keenan (2006) [39]

Abbreviation is as follows: SDS-PAGE, sodium dodecyl sulphate polyacrylamide gel electrophoresis.

needs to demonstrate equivalent average pharmacokinetic properties compared with the originator drug. Bioequivalence is achieved, and hence therapeutic equivalence is presumed, if the mean ratios for key pharmacokinetic parameters (maximal plasma concentration and area under the concentration–time curve) of the generic drug vs. the originator have a 90% confidence interval (CI) within 0.80 and 1.25 of the originator in healthy volunteers; for some NMRAs, narrower ranges may apply for some drugs with a narrow therapeutic index. Even bioequivalence may not be met in some developing countries that do not have the necessary quality-assurance resources or regulations. A case reported in Greece highlighted the fact that problems may also occur in the manufacturing of generics in developed countries. Following an increase in postoperative infections in patients receiving generic cefuroxime compared with patients receiving the originator drug, analysis of the generic version (manufactured in Greece) revealed a substandard formulation [69]. It should also be noted that in some cases, a ‘generic’ might in fact be a ‘copy drug’, i.e. a version of the drug that, although it is available on the market, has not undergone

any bioequivalence testing. This was thought to be the case for a substandard version of imatinib manufactured in India, for which no regulatory documentation was evident [70].

Excipients used in a generic formulation are not required to be identical to those in the originator formulation. Small changes in excipients can alter the properties of a formulation (e.g. lead to differences in particle size, or modify the shelf-life) and hence affect drug efficacy and safety. For example, although excipients such as polysorbate 80 and polyoxyethylated castor oil are considered inert, some investigators have reported evidence of altered drug metabolism with changes in the source of such compounds [71, 72].

The testing of a drug’s dissolution properties is a relatively simple *in vitro* test used as an indicator of *in vivo* bioavailability. Drug-specific limits for dissolution times are defined in pharmacopoeias, against which samples can be compared. This might be used, for example, to check batch samples of a branded drug or to compare generic versions against originator drugs. There are many examples in the published literature in which studies have

shown marked variation in dissolution times between supposedly bioequivalent drugs (Table 3 [12, 17, 19, 26, 33, 35–37, 55, 56, 73–87]). For example, testing of five generic versions of tacrolimus available in Mexico demonstrated considerable differences in their dissolution profiles compared with that of the branded originator drug [33]. In another study, approximately one-third of samples of a variety of antimalarial drugs acquired in Africa failed to meet the USP dissolution specifications [19].

Stability of a formulation in a variety of storage conditions is also an important issue, particularly in tropical settings. Dissolution tests performed after simulation of tropical conditions can reveal drug deterioration. For example, an analysis of chloroquine phosphate tablets marketed in Tanzania found that the reference formulation and one of the six generic products tested failed to meet the USP dissolution specifications after 6 months of stability testing (Table 3) [74]. Some drugs appear to be inherently unstable and potentially unsuitable for use in tropical conditions. For example, concerns have been raised regarding the WHO's recommendation of dihydroartemisinin-containing antimalarial combination drugs [88]. Although dihydroartemisinin is an effective antimalarial agent, it has been shown to fail accelerated stability tests [88]. The WHO has issued recommendations for appropriate stability testing when drugs are to be distributed in countries with tropical climates [89]. Appropriate storage facilities may also be required; for instance, a study in Brazil found that some state storerooms and basic health units in the north of the country provided inadequate storage for antimalarials, given the area's conditions of high temperature and high humidity [90].

Drug stability can be influenced by packaging, and appropriate packaging is particularly important in conditions such as high humidity, heat or strong light. A study by Singh and Mohan found that, under accelerated stability testing, blister-packed fixed-combination antituberculosis products were prone to physical and chemical changes not observed with strip-packed counterparts [81]. Analysis of the unpacked products showed decomposition of the rifampicin component, highlighting the potential consequences if the packaging was not sufficiently robust. Unfortunately, issues such as packaging are not as tightly controlled as drug content, and packaging of generic products in particular may be less able to withstand certain storage conditions.

Even in developed countries, there is a lack of appreciation of the importance of packaging of generic products. For example, in a recent review, Zore *et al.* note the influence of the bottle tip design on the dose of topical ophthalmic preparations delivered to the eye, with drop size varying substantially between generic manufacturers of eye drops and causing different amounts of drug to be delivered to the eye [91].

The advent of biosimilars [92] has also necessitated the development of new guidelines specifically for such

products and will be another area requiring careful regulation and monitoring. The FDA has published draft guidelines on biosimilar product development [93], while the EMA has issued general guidance and guidelines for specific drugs [94]. Other countries, including Japan, India, Canada, Mexico, Brazil, Malaysia and Australia, have also issued guidelines for registration of biosimilars.

Potential consequences of substandard drugs

Substandard drugs pose a serious health concern from several perspectives (Table 4 [47, 48, 51, 52, 57, 59, 70, 95–104]). Although falsified drugs have perhaps received most of the attention with respect to causing unnecessary deaths, substandard drug manufacture also leads to morbidity and mortality. A formulation with insufficient API may lead to a lack of clinical response, and possibly, death. For example, there are reports of patients failing to respond to antimalarial treatment [95, 96] because the drugs contained less than the stated dose of API and, in one reported case, contained more paracetamol than antimalarial agent [95]. In other cases, a reduced therapeutic response has been associated with generic/copy versions of drugs compared with the originator drugs, including antibiotics, tacrolimus and imatinib [70, 97, 99–102].

Adverse events also occur due to drug–drug interactions with contaminants, the presence of excess API, contamination with poisonous substances, or allergic reactions to contaminants or substituted excipients. As mentioned above, some of the most extreme cases involve the (possibly deliberate) contamination of medicines with DEG [47, 48]. In another case, heparin was found to be contaminated with oversulphated chondroitin sulphate, which was thought to be responsible for the allergic or hypersensitivity-type reactions experienced by a number of patients, some of which proved fatal [51]. At the time of the heparin incident, the oversulphated chondroitin sulphate could not be distinguished from heparin by the standard quality-control tests used. However, the FDA has since implemented changes to the USP standards for heparin, including a new test method that is able to detect such impurities [105].

There are also adverse societal effects arising from the use of substandard drugs. The inadvertent use of suboptimal doses of drugs is likely to be one of the key factors contributing to antimicrobial resistance and thereby leading to the wider spread of disease. This has been most widely discussed with regard to malaria [106–108]; the repeated administration of subtherapeutic doses of antimalarials will promote the selection and spread of resistant parasites [95, 106]. Indeed, artemisinin-resistant malaria has been reported in Cambodia and Thailand [109, 110],

Table 3

Substandard drugs: pharmacological variability

Drug(s)	Issue	Region/countries	Reference
Antimalarials			
Chloroquine phosphate	Significant differences in bioavailability between two different formulations	Tanzania	Rimoy <i>et al.</i> (2002) [73]
Chloroquine phosphate	One locally sourced formulation and the reference formulation failed to meet the USP dissolution specifications after 6 months in simulated tropical conditions	Drugs from China, Tanzania and India available in Tanzania; reference drug from Belgium	Risha <i>et al.</i> (2002) [74]
Sulfadoxine-pyrimethamine	Two of three locally available drugs failed USP requirements for dissolution at time of purchase	Drugs from Kenya, Tanzania and India; reference drug from Switzerland	Risha <i>et al.</i> (2002) [74]
Amodiaquine and sulfadoxine-pyrimethamine	13% (<i>n</i> = 15) of amodiaquine and 44% (<i>n</i> = 18) of sulfadoxine-pyrimethamine samples failed the dissolution test, based on USP criteria	Tanzania	Minzi <i>et al.</i> (2003) [12]
Sulfadoxine-pyrimethamine and amodiaquine	40.5% (<i>n</i> = 116) of samples did not meet USP specifications for content and/or dissolution	Kenya	Amin <i>et al.</i> (2005) [17]
Artesunate, chloroquine, quinine, mefloquine, sulfadoxine-pyrimethamine and tetracycline	1.9% (<i>n</i> = 53) of artesunate, 10.5% (<i>n</i> = 86) of chloroquine, 4.5% (<i>n</i> = 88) of quinine and 1.1% (<i>n</i> = 93) of tetracycline samples failed disintegration tests	Thailand	Vijaykadga <i>et al.</i> (2006) [75]
Quinine, chloroquine, sulfadoxine-pyrimethamine and mefloquine	46% (<i>n</i> = 28) failed to meet the USP dissolution standards	Congo, Burundi and Angola	Gaudio <i>et al.</i> (2007) [76]
Sulfadoxine-pyrimethamine, amodiaquine, mefloquine, artesunate, artemether, dihydroartemisinin and artemether-lumefantrine fixed-dose combination	35% (<i>n</i> = 210) of samples tested failed dissolution tests	Africa	Bate <i>et al.</i> (2008) [19]
Antifolates (sulfadoxine-pyrimethamine, sulfamethoxy-pyrazine-pyrimethamine), amodiaquine, quinine and artemisinin derivative samples	12.2% (<i>n</i> = 304) of formulations analysed failed to meet USP specifications for dissolution; this included 23.8% of quinine tablets Amodiaquine samples were generally of better quality	Tanzania	Kaur <i>et al.</i> (2008) [77]
Antiretrovirals			
Triomune-40 (fixed-dose combination of stavudine, lamivudine and nevirapine)	Generic formulation was not bioequivalent to branded version	Malawi	Hosseinpour <i>et al.</i> (2007) [78]
Antituberculosis drugs			
Rifampicin	One of three locally manufactured drugs had lower bioavailability in 12 patients (ratio 0.86) compared with the reference standard	Indonesia	van Crevel <i>et al.</i> (2004) [79]
Rifampicin in FDC products	Rifampicin bioavailability reduced in seven of 10 FDC products vs. individual formulation Subsequent study showed that FDCs were inadequately packaged, leading to drug deterioration	South Africa/India	Pillai <i>et al.</i> (1999) [80]; Singh and Mohan (2003) [81]
Other antibiotics			
Cefuroxime	Generic formulation unstable; rapidly hydrolysed into two ineffective molecules	Greece	Mastoraki <i>et al.</i> (2008) [69]
Clarithromycin	34% (<i>n</i> = 50) of generics tested released less drug in 30 min than the reference (Abbott) Only one generic did not meet Abbott's specification (80% must dissolve within 30 min)	Multinational (18 countries)	Nightingale (2005) [26]
Ofloxacin	Antibacterial disc diffusion zone diameters varied significantly between different products (<i>n</i> = 34)	Pakistan	Iqbal <i>et al.</i> (2004) [82]
Immunosuppressants			
Tacrolimus	Compared with branded Prograf, generic Tacrobell and T-Inmun exhibited faster dissolution; Tenacrine, Framebin and Talgraf showed slower and incomplete drug dissolution, releasing 24–51% of tacrolimus within 2 h Solubility of generics was decreased relative to Prograf	Mexico	Petan <i>et al.</i> (2008) [33]
Mycophenolate sodium	At pH 6.8, mean mycophenolate sodium release with Myfortic (reference) was 104.9% compared with 62.3% for the generic Femulan (<i>P</i> = 0.04) Six samples were tested from a single batch of each formulation There was intratablet variability with Femulan	Mexico	Esquivel <i>et al.</i> (2010) [83]

Table 3

Continued

Drug(s)	Issue	Region/countries	Reference
Cardiovascular Clopidogrel	Two of 18 generics failed the dissolution test according to USP and Sanofi-Aventis specifications	Multinational (five countries)	Gomez <i>et al.</i> (2004) [56]
Carvedilol	Eleven of 35 generics did not meet dissolution criteria (<75% in 30 min) specified by the European Pharmacopoeia and Roche	Multinational (19 countries)	Smith <i>et al.</i> (2006) [35]
Simvastatin	Five of 19 generics failed to meet USP specifications for dissolution There was significantly more variability among generics produced outside the USA	Multinational; based on Internet availability of generics	Veronin and Nguyen (2008) [84]
Antihypertensives Ramipril	Eight of 10 test formulations were substandard for combined tests of content/dissolution 24% (<i>n</i> = 21) of generics/copies failed to meet the reference ramipril product specifications for dissolution (≥80% dissolved in 30 min) The failure rate increased to 57% after storage for 3 months	Rwanda Italy	Twagirumukiza <i>et al.</i> (2009) [36] Angeli and Trezza (2009) [37]
Analgesics Acetylsalicylic acid tablets	Three of three samples failed to meet USP dissolution specifications	Drugs from Tanzania and Kenya available in Tanzania	Risha <i>et al.</i> (2002) [74]
Paracetamol tablets	Two of nine samples failed to meet USP dissolution specifications at purchase; five of nine failed after 3 months in simulated tropical conditions	Drugs from India or Tanzania, available in Tanzania	Risha <i>et al.</i> (2002) [74]
Diclofenac sodium	In simulated intestinal medium, four of 16 national brands did not meet USP specifications of 80% drug release in 8 h Five national brands, defined as substandard, demonstrated first-order release kinetics as opposed to zero-order kinetics specified by USP	Bangladesh	Abdullah <i>et al.</i> (2008) [85]
Antidiabetics Glimepiride	52% of generics (<i>n</i> = 23) failed to meet branded Amaryl specifications for dissolution (≥85% dissolved in 15 min)	Italy	Attorse and Massi-Benedetti (2007) [55]
Other β-Blocker and α-agonist eye drops for glaucoma	Generics (five samples of six products) varied significantly from branded equivalents (five samples of five products) in drop volume, viscosity, surface tension and bottle orifice diameter; for example, generic timolol products delivered 37–40% less drop volume and daily prescribed dosage than branded versions	USA and Canada	Mammo <i>et al.</i> (2012) [86]
Octreotide	Comparison of Sandostatin® LAR® with three other versions of depot octreotide formulations showed variations in microparticle size, shape, molecular weight and acid:base ratio, suggesting different drug-release patterns	Not stated	Petersen <i>et al.</i> (2011) [87]

Abbreviations are as follows: FDC, fixed-dose combination; USP, United States Pharmacopoeia.

although the extent to which this can be attributed to the use of substandard drugs is unknown. Likewise, poor-quality antibiotics may contribute to the resistance and spread of diseases such as tuberculosis [23, 111, 112]. The use and subsequent failure of substandard narrow-spectrum antibiotics may lead to the unnecessary administration of broad-spectrum antibiotics, thus potentially creating further resistance [113]. Substandard antihelminthics have been implicated in the development of drug-resistant human helminths [114], and substandard antiviral drugs are likely to contribute to the evolution of drug-resistant viruses, including human immunodeficiency virus (HIV) [115].

In developed countries, the impact of poor-quality antimicrobials on drug resistance may be seen as being minimal, with overuse considered to be the key factor. This

is exemplified by the recently published 'threat report' from the US Centers for Disease Control and Prevention, which highlights the urgent issue of antibiotic resistance and presents 'four core actions to prevent antibiotic resistance'; the potential contribution made by substandard drugs is not discussed [116]. However, in the modern world, what is initially geographically localized drug resistance can rapidly become a global issue and should be taken into account in strategies to limit drug resistance. The potential for administration of substandard drugs to contribute to antimicrobial resistance has been recognized by the WHO, which lists 'inadequate systems to ensure quality ... of medicines' as one of the underlying factors that hasten the emergence and dissemination of antimicrobial resistance [117]. A greater understanding of the prevalence, distribution and type of quality issues

Table 4

Examples of adverse outcomes associated with substandard drugs

Drug(s)	Adverse outcome	Cause	Region/countries	Reference
Miscellaneous				
Paracetamol, cough expectorant, propolis, teething syrup, armillarisin, sulfanilamide, sedatives and silver sulfadiazine	Gastrointestinal symptoms, metabolic acidosis, renal injury, neuropathies and death	Diethylene glycol contamination	Nigeria, USA, Panama, South Africa, India, Spain, Bangladesh, Argentina, Haiti and China	Schep <i>et al.</i> (2009) [48]; Schier <i>et al.</i> (2009) [47]
Antimalarials				
Artesunate	One patient died due to cerebral malaria despite treatment with oral artesunate	Subsequent analysis of the drug found that although artesunate was present, the main API was paracetamol. The drug was traced to a fake batch purchased in good faith by the hospital	Burma	Newton <i>et al.</i> (2006) [95]
Artemether	No clinical response was observed after 5 days of treatment with artemether (one patient)	The used vial contained only 74% of the manufacturer's stated dose	Lao People's Democratic Republic	Keoulangkhot <i>et al.</i> (2008) [96]
Sulfadoxine-pyrimethamine	An <i>in vivo</i> failure rate of 28.5% was documented at a refugee camp with an outbreak of malaria	Locally manufactured sulfadoxine-pyrimethamine was substandard, i.e. it did not meet tolerance limits for dissolution	Pakistan	Leslie <i>et al.</i> (2009) [97]
Antibiotics				
Cefuroxime	Generic cefuroxime ($n = 305$ patients) was compared with original cefuroxime ($n = 313$ patients) as antimicrobial prophylaxis in patients undergoing coronary artery bypass grafting surgery; 12.8 vs. 2.5% of patients experienced postoperative infections with generic vs. original cefuroxime, respectively ($P < 0.001$)	Unstable formulation	Greece	Mastoraki <i>et al.</i> (2008) [69]
Anticoagulants				
Heparin	Allergic or hypersensitivity-type reactions (some fatal) in patients treated with heparin that was imported from China and subsequently found to be contaminated with oversulphated chondroitin sulphate	Contaminant not removed in production process	USA and Germany	Blossom <i>et al.</i> (2008) [51]; Food and Drug Administration (2009) [98]
Heparin	162 cases of <i>Serratia marcescens</i> bloodstream infection	The infection was traced to prefilled syringes	USA	Blossom <i>et al.</i> (2009) [52]
Cardiovascular				
Isosorbide-5-mononitrate tablets	More than 120 deaths	Contamination with antimalarial drug pyrimethamine due to a manufacturing error	Pakistan	Attaran <i>et al.</i> (2012) [57]; World Health Organization (2012) [59]
Immunosuppressants				
Tacrolimus	Use of generic version associated with higher rate of acute kidney rejection than use of original Prograf formulation (20.8 vs. 11.8%; $P = 0.08$)		Mexico	Holm and Hernandez (2008) [99]
Oncology				
Imatinib	Several case reports of patients with CML who achieved a complete or partial haematological response on Glivec, lost the response when switched to a copy version, but regained response when switched back to Glivec		India, Egypt and Morocco	Goubran (2009) [70]; Mattar (2010) [100]; Asfour and Elshazly (2009) [101]; Chouffai (2010) [102]
Steroids				
Methylprednisolone acetate	478 cases of fungal meningitis (including 34 deaths) and 12 peripheral joint infections	<i>Exserohilum rostratum</i> contamination in steroid injections	USA	Centers for Disease Control and Prevention (2012) [103]; Kainer <i>et al.</i> (2012) [104]

Abbreviations are as follows: API, active pharmaceutical ingredient; CML, chronic myeloid leukaemia.

affecting antimalarial drugs is also a key aspect of the WorldWide Antimalarial Resistance Network's efforts to monitor the development and spread of malaria drug resistance [118].

Some of the most obvious examples of potential societal, as well as individual, harm come from the use of substandard vaccines. As documented by Kelesidis and colleagues, there have been incidences in which 'vaccines' have contained only water. A notorious case occurred in Niger, where over 50 000 people received falsified meningitis vaccine during a meningitis epidemic in 1995; 2500 people died, and many were permanently handicapped [119].

In addition to these clinical outcomes, being treated with substandard drugs is likely to result in a loss of confidence in medication by both the prescribing physician and the patient. Effective drug classes may be perceived to be ineffective due to inadvertent suboptimal dosing, potentially leading to unnecessary testing for suspected resistance [97] and to unnecessary drug switching or augmentation.

All of the above clinical and humanistic factors contribute to an increased economic burden, both on a national scale and to individuals. In some developing countries, up to 90% of the population have to pay for their medicines, and these costs can account for a large proportion of household income [120]. Paying for replacement or additional drugs, or for repeated courses of inadequate ones, may impose a severe economic burden on a household, especially if combined with loss of income due to illness. At a national level, the costs associated with inadequate or contaminated drugs may include those for lost productivity, in addition to increased direct healthcare costs if these are at least in part met by the state. As noted by Wertheimer and Norris, development of resistance secondary to the use of commonly available (often generic) drugs will necessitate the development of new, probably more expensive alternatives, thus further aggravating the economic burden of treating infectious diseases [115].

How prevalent are substandard drugs?

The true extent of the problem is unknown but can occur worldwide (Figure 1). A few published reviews by investigators and reports by international bodies, such as the WHO, have collated information from individual studies or a range of countries to try to gain an overview of the prevalence of substandard drugs, particularly antimicrobials, in developing countries [1, 119, 121, 122]. For example, a comprehensive review published by Kelesidis and colleagues highlighted the extent of the problem of 'counterfeit/substandard' antimicrobial drugs, particularly in southeastern Asia and Africa [119]. This apparent geographical bias reflects the poorer regulatory control in

these areas. The authors also highlight the fact (as also shown in Tables 1–3 in this article) that although there have been reports of falsified or substandard drugs in many pharmacotherapeutic groups, antibiotics and antiparasitic drugs appear far more likely to be falsified than other drugs [119].

In 2006, the WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) estimated that in parts of Africa, Asia and Latin America, more than 30% of drugs on sale could be falsified [123], although the sources for this statistic are unclear. The UK charity Oxfam has branded such statistics as 'dubious', as they appear to be based on anecdotal reports [124].

Much of the attention in the past has focused on the problem of deliberately falsified drugs, but even in this area the figures are vague. Governments and the pharmaceutical industry have been criticised previously for being reticent to make knowledge about falsified drugs public [125]. The figure of 10% of marketed drugs being falsified is frequently quoted and has been attributed to the WHO and to the FDA [124, 126, 127]. However, the origin of this statistic (as pointed out in a *Wall Street Journal* article [128]) may be in a 2002 *British Medical Journal* editorial [126] that misquoted an earlier WHO report. Although the WHO has used the figure in factsheets, it has since refuted it via IMPACT [123].

The problem of patient exposure to substandard drugs is not confined to developing countries, although IMPACT estimated that the prevalence of falsified medicines would be less than 1% of sales in most developed countries with adequate regulatory systems and market control [123]. A search of the UK's MHRA website revealed that between December 2005 and October 2012, 211 drug alerts were issued, including 22 Class 1 (critical) alerts for problems such as falsified drugs, incorrect drug quantities, packaging issues and contamination [129]. Between March 2011 and November 2012, approximately 40 company-led recalls were also issued for problems including contamination, inadequate stability and labelling or packaging concerns. The country of origin of the drugs concerned was not stated.

Substandard medicines are also sold via the Internet, thus potentially affecting a wide patient population. The WHO has estimated that over 50% of medicines purchased via the Internet from sites that conceal their physical address are falsified [8] although, again, the evidence for this is not clear. However, an analysis of selected drugs purchased from a range of website pharmacies found that, with the exception of Viagra®, the drugs met quality standards [130]. Phosphodiesterase type 5 inhibitors (i.e. sildenafil, tadalafil and vardenafil) are the drugs most likely to be falsified [131] and so are probably the most common falsified drugs to be sold via the Internet. Contaminants in falsified sildenafil have included talcum powder, paint and a range of APIs [131]. Conversely, it has been reported that a 'natural' herbal product sold as a remedy for impotence

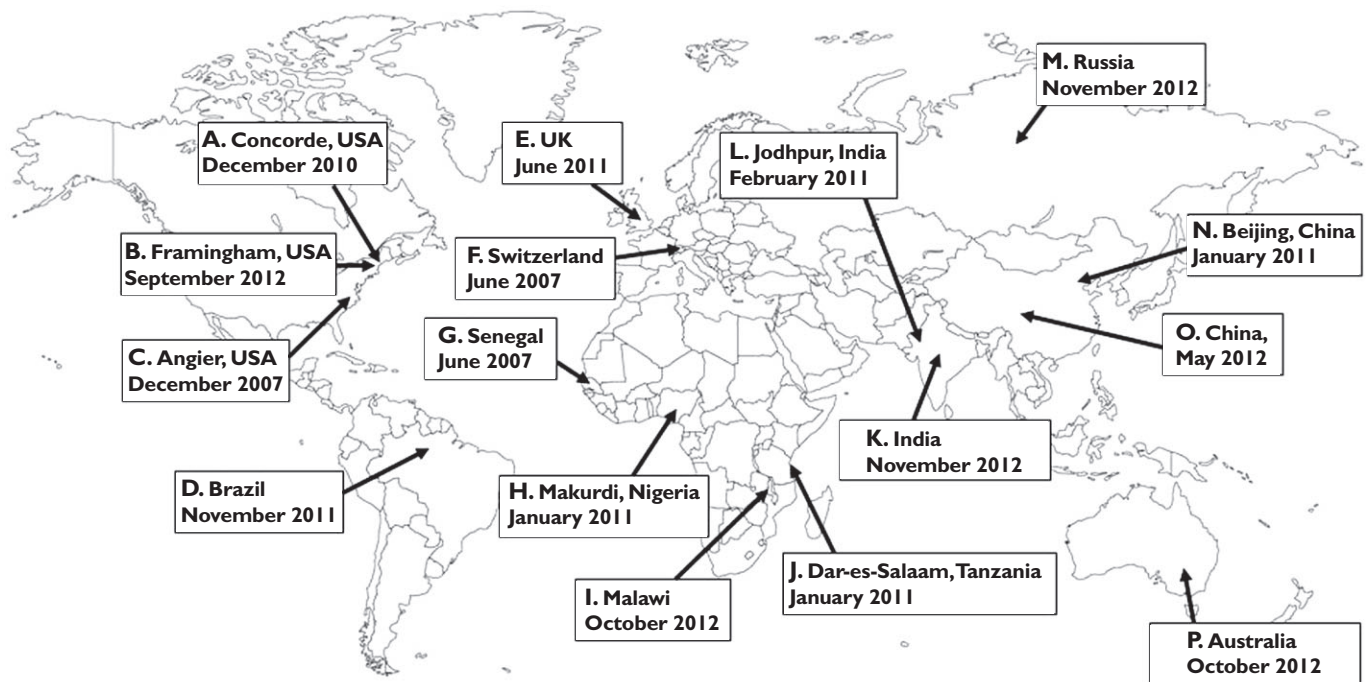


Figure 1

Examples of recent accounts of substandard drugs around the world. (A) GlaxoSmithKline fined because four drugs it marketed did not meet US Food and Drug Administration's strength and purity standards (Boston.com). (B) Outbreak of fungal meningitis traced to contaminated methylprednisolone injections produced by the New England Compounding Center [103]. (C) Five deaths and 300 people infected due to distribution of contaminated prefilled heparin and saline syringes by AM2PAT (The Institute for Southern Studies, 2009). (D) Defects in quality of antimalarial drugs held at national and state facilities [90]. (E) Plasticizers, including diisodecyl phthalate and diisononyl phthalate, found in Augmentin formulations manufactured in the UK; products recalled in Hong Kong and China (The Telegraph/FiercePharma). (F) Ethyl mesylate contamination of nelfinavir at Roche's Swiss manufacturing plant (National AIDS Manual, 2007). (G) Ghana's medicines regulatory authority ordered Pfizer to recall substandard Camoquine-plus suspension manufactured in Senegal and distributed in Ghana (Ghana News Agency). (H) Nigeria's National Agency for Food and Drug Administration raided pharmacies and other outlets and impounded a variety of drugs believed to be falsified (Nigerian Tribune). (I) Pharmacy, Medicines and Poisons Board recalled aspirin tablets on suspicion of being substandard (Malawi News). (J) The Tanzania Food and Drugs Authority suspended importation, distribution, sale and use of nine types of medicines found to be substandard (The Citizen, Tanzania). (K) As of November 2012, almost 300 drugs have been listed as being found to be substandard in 2012 (DrugsControl.org, India). (L) Thirteen women died in little over a week due to contaminated intravenous fluids. No system was in place for testing or checking medicines (The New Indian Express). (M) Russia's Federal Service on Surveillance in Healthcare (Roszdravnadzor) discovered and removed 530 series of 'low-quality' drugs from circulation in 2012; over 70% of these were produced by domestic manufacturers (HIS Global Insight/Rossiyskaya Gazeta). (N) Six hundred and sixty-nine batches of gel capsules from 254 drug manufacturers were found to have high chromium levels (30 May 2012; FiercePharmaManufacturing). (O) More than 60 tonnes of fake and substandard pharmaceuticals and medical equipment were destroyed by Beijing's municipal drug supervision bureau (People's Daily Online). (P) Batches of Typhim Vi vaccine were recalled because they may have lower than expected antigen content (Therapeutic Goods Administration)

actually contained sildenafil [132]. The standards of packaging and labelling of drugs sold via the Internet has also raised concerns [133].

With regard to the distribution of poor-quality genuine medicines that have resulted from deficiencies in the manufacturing process, there are isolated published reports, press articles, as well as recall information made available by national authorities, but there are no definitive statistics regarding the scale of the overall problem. If systems are not in place to make manufacturers assess and report such defects and to make the regulatory bodies manage the drug recall, there is considerable scope for harm. The scale of such incidents in countries with poor or non-existent fail-safes is, of course, unknown.

How can drug quality be improved?

There are two separate, albeit related, issues in preventing the dissemination of substandard drugs. One is combating the trade in falsified drugs from a legal perspective. The other is ensuring adequate quality at the drug manufacture and quality control levels for both branded and generic drugs alike. While many steps are being taken to ensure the authenticity of marketed drugs, including the approval of new legislation by the European Parliament [134], these do not necessarily address the wider issue of controlling drug quality. There are many levels at which drug quality monitoring and regulation can be improved. A full discussion of

the potential research activities and possible solutions that could be implemented by academics, regulators and manufacturers is beyond the scope of this article, and readers are encouraged to consult recent comprehensive reviews of these topics [10, 135–137]. Some of the key requirements and initiatives for combating the distribution of substandard drugs will be discussed below.

Better understanding of the problem

There is an urgent need for greater understanding of the problem, in particular through better systematic collection and accurate, transparent documentation of information on substandard drug manufacture and dissemination. This would help inform national authorities about the scale of the problem and provide a database against which batches of drugs could be checked. In addition, it may help in assessing the true degree of local drug resistance to, for example, antimalarials. The paucity of accurate data is highlighted by the oft-quoted but rather doubtful ‘statistics’ on substandard drugs, as discussed earlier. While some information is documented in peer-reviewed journals (as shown above) or official reports, much of our current awareness of the problem of substandard drugs is due to press reports, Internet articles and anecdotal accounts. An interesting contrast can be made with the effort expended on trying to combat ‘illicit’ drug distribution (where such drugs usually comprise narcotics, stimulants, sedatives, hallucinogens and cannabis, i.e. drugs of abuse for the want of a better term). National governments commit substantial amounts of money to investigate and prevent illicit drug production. Each year, the United Nations issues a large ‘World Drug Report’ that includes extensive statistics on production and consumption of such drugs and analyses of the economic burden of illicit drug use [138]. The issue of substandard drugs is probably a much larger problem, and affects more people, therefore surely warranting similar attention.

Carefully conducted surveys with precise targets and incorporating standardized testing could be used to help define the extent of the problem. For example, an ongoing study has been established by the WHO and the Drug Quality and Information Program on the quality of antimalarial medicines in 10 Sub-Saharan countries (the QAMSA study). Antimalarial drug samples are obtained from both the regulated and ‘informal’ market and tested using the Global Pharma Health Fund Minilab® kit and/or full USP laboratory analysis. Initial findings have shown that 44% of sampled antimalarial medicines in Senegal failed to meet USP quality standards. The failure rates in Madagascar and Uganda were 30 and 26%, respectively [139]. Minilab testing (444 samples) showed that 43, 12 and 6% of samples in Senegal, Uganda and Madagascar, respectively, failed quality assessments. A similar QAMSA survey in Cameroon, Ethiopia, Ghana, Kenya, Nigeria and Tanzania found that of 267 tested antimalarial drug samples, 28.5%

failed to comply with specifications, with the proportions ranging from 0% in Ethiopia to 64% in Nigeria [140].

The International Medical Products Anti-Counterfeiting Taskforce was launched by the WHO in 2006 with the aim of detecting and preventing the production and sale of ‘counterfeit’ medicines. However, this project has been criticised by member states, and most notably in a recent report issued by Oxfam, for apparently focusing on enforcing intellectual property rights in order to prevent criminal trademark-infringement activities (i.e. prevent the distribution of falsified drugs), rather than trying to combat the wider issues of falsified drugs or the substandard manufacture of legally produced and marketed drugs [124]. Oxfam has also criticised IMPACT for causing ‘unnecessary confusion’ by misusing the term ‘counterfeit’ to refer to ‘substandard and falsified medicines that are unrelated to criminal trademark infringement’. Oxfam has called for IMPACT to be disbanded [124]. At the 63rd World Health Assembly in May 2010, it was decided to create a ‘time-limited and results-oriented working group on substandard/spurious/falsely labelled/falsified/counterfeit medical products (SSFFC) comprised of and open to all member states’. The remit of the working group would include investigating IMPACT. Progress has been slow, much to the concern of several countries, particularly India [141]. However, in May 2012 a Member State Mechanism was approved for international collaboration to prevent and control SSFFC [142], and the first formal meeting was held in November 2012.

In 2009, the US Agency for International Development (USAID) and USP jointly set up the Promoting the Quality of Medicines programme, aimed at ensuring the quality, safety and efficacy of medicines in USAID’s health programmes. In April 2011, in collaboration with authorities in Africa, South America and Southeast Asia, the Promoting the Quality of Medicines programme launched the Medicines Quality Database [143], which reports on the quality of a variety of medicines collected in these regions.

The WorldWide Antimalarial Resistance Network has recognized the paucity of high-quality published data on the topic of substandard drugs and has established a pilot database of reports on antimalarial drug quality [118]. Most recently, as part of its ongoing aim to collate information on the prevalence and distribution of poor-quality antimalarials around the world, the Antimalarial Quality Scientific Group of the WorldWide Antimalarial Resistance Network launched an online interactive antimalarial-quality surveyor, which maps reports of antimalarial quality from a variety of sources [144, 145].

Improved regulatory control and monitoring

Key to the improvement and maintenance of drug quality is the implementation of strong regulatory control. There is a need for pharmacovigilance programmes to be in place in order to monitor the safety of marketed drugs

constantly and to communicate any safety issues to manufacturers, healthcare providers and patients.

The level of such control varies widely. In the USA, for example, minimal Good Manufacturing Practice standards are defined by the FDA and upheld by law. In many other countries, there is negligible control. Caudron and colleagues even noted that manufacturers may run parallel production processes, adjusting their standard according to that of the recipient country [1]. The WHO estimates that only approximately 20% of its 191 member states have well-developed drug regulation; approximately 30% are thought to have no or minimal drug regulation in place [146]. It should also be borne in mind that the standards set by different NMRAs may vary and may not meet international standards. The survey conducted by the WHO in six Sub-Saharan countries found that 14% of collected antimalarial drug samples were not registered by the NMRA [140]. Worryingly, in Pakistan the pharmaceutical industry has been operating without formal control since the national Ministry of Health was abolished in June 2011 and its power devolved to the provinces. However, following the deaths in January 2012 of over 100 patients in Lahore due to contamination of the antianginal agent Isotab® (isosorbide mononitrate 20 mg) with the antimalarial pyrimethamine, the government of Pakistan established the Drug Regulatory Agency to regulate the country's pharmaceutical industry [59, 147].

The WHO has implemented a number of programmes to try and address the problem of substandard drugs. One is the prequalification programme, established in 2001 on behalf of the United Nations, which aims to ensure access to medicines that meet specified standards of quality, safety and efficacy, mainly for HIV/AIDS, malaria, tuberculosis and reproductive health [148]. Candidate products and their manufacturing sites are assessed by stringent regulatory bodies. Those that pass are placed on a list that can be used by international agencies such as UNICEF, as well as by national agencies requiring guidance. The prequalification programme regularly re-inspects manufacturing sites of prequalified products to ensure the continued safety of such products. The WHO survey of antimalarial drug quality in six Sub-Saharan countries noted that, while the overall failure rate was almost 30%, only 4% of samples of prequalified medicines failed testing and, in each case, the deviation was considered minor [140]. However, as has been pointed out by others, the list of prequalified drugs for HIV/AIDS issued by the WHO includes a disclaimer stating that 'Inclusion in the list does not constitute an endorsement, or warranty of the fitness, by WHO of any product for a particular purpose, including in regard of its safety and/or efficacy in the treatment of HIV/AIDS' [149], which raises questions about the value of the programme. It is also worth noting that the WHO has approved a 'biowaiver' procedure, whereby it accepts evidence of equivalence other than *in vivo* equivalence testing [150].

The Good Governance for Medicine programme was set up by the WHO in 2004 to help combat corruption in the pharmaceutical sector and is currently operating in 26 countries [151]. The programme comprises a three-phase approach, covering assessment, development and implementation of national Good Governance for Medicine programmes. Using a standardized assessment instrument [152], the first phase of the programme in any country involves a national assessment of transparency and potential vulnerability to corruption in different aspects of drug production and marketing. These aspects include the following: registration of medicines and control of their promotion; inspection and licensing of establishments; selection, procurement and distribution of essential medicines; and control of clinical trials. A recent report into five countries noted deficiencies in the areas of 'management of conflict of interest with regard to inspection activities' and 'written procedures or mechanisms to prevent personal relations between an inspector and the manufacturers or distributors', among others [153]. However, these findings are only of value if action is taken by the individual countries to revise their existing policies and enforce good governance. The WHO reports a number of successes for the programme but emphasizes that high-level government commitment is required [154].

In addition to monitoring of drug products, more stringent control is needed for the quality of APIs. A press report from India noted that, despite regulations being introduced in 2003 to curb the import of substandard raw materials, customs authorities seized several consignments of substandard materials imported by traders. The ingredients were believed to have entered the country through smaller ports, where 'customs scrutiny was less stringent' [155]. In 2010, the WHO's prequalification programme was extended to include a pilot scheme for prequalification of selected APIs for products for treating HIV and related diseases, for antimalarial medicinal products and for antituberculosis products [156], but wider regulation is still required.

In Africa, Nigeria's National Agency for Food and Drug Administration (NAFDAC) has provided a model for how to improve the provision of safe medicines. Since 2001, it has implemented a series of measures to combat falsified and poor-quality drugs and to ensure drug safety. In 2001, a survey estimated that 68% of the drugs available in Nigeria were not registered with NAFDAC; by 2004, this level had been reduced by 80% [157]. The actions of NAFDAC include recommendations for changes in the law, dismissal of corrupt NAFDAC personnel, guidelines for staff behaviour and use of incentive schemes for NAFDAC staff, destruction of large quantities of falsified and expired drugs, strict enforcement of registration guidelines, implementation of new guidelines to ensure that imported drugs are genuine, and raising public awareness of falsified drugs, including publication of lists of identified fake/substandard products in newspapers [157–159]. A review

conducted in 2007 using the WHO's Good Governance for Medicine assessment tool found that the pharmaceutical sector in Nigeria was still vulnerable to corruption and that the greatest weakness was the lack of conflict-of-interest guidelines [160].

The NAFDAC, in partnership with some pharmaceutical companies, has also tested and adopted an innovative new mobile authentication service developed by a US company (Sproxil) to help ensure that only genuine drugs reach the consumer. This comprises a scratch panel added to the drug package; the consumer scratches the panel to reveal a code, which can then be sent in a text message to the authentication service. A message is sent back confirming whether or not the drug is genuine. The service is free for consumers [161, 162]. In January 2012, Sproxil announced that the verification service had been used to check medicines more than one million times in Africa [163]. The system is also being adopted in India and Kenya.

Other regions and countries have implemented initiatives to prevent the distribution of substandard drugs, although these are mainly aimed at detecting falsified drugs. For example, the Directorate General of Foreign Trade in India is currently implementing a barcode-based 'track and trace' system, to help prevent the export of substandard drugs [164, 165].

As mentioned above, the European Parliament will call for new safety features to be applied to individual packs of drugs in order to 'identify them, guarantee their authenticity, and enable pharmacists to check whether the outer packaging has been tampered with' [134]. Member states will also be required to implement a system to prevent medicinal products that are 'falsified and with quality defects' from reaching the patient. The European Falsified Medicines Directive [134] came into force in January 2013, with the aim of improving the monitoring of the supply chain for medicinal products and active substances. The Directive includes the use of unique identifiers on packs of medicines. Tracking systems are being developed and tested by the European Federation of Pharmaceutical Industries and Associations [166] and the European Directorate for the Quality of Medicines and Healthcare [167]. In the USA, the FDA has been in discussion with pharmaceutical companies regarding the instigation of a 'track and trace' system, but this is likely to be delayed by cost concerns.

The European Falsified Medicines Directive also includes development of guidelines for good distribution practices for medical products and APIs. The European Commission [168] has revised its good distribution practice guidelines for medical products and established a new database (EudraGMDP) to facilitate the checking of information on manufacturers, importers and distributors of APIs. Draft guidelines covering APIs have also been issued recently by the European Commission [169]. Even in developed countries, the issue of poor-quality APIs has caused problems and is being addressed by tighter control and

international agency cooperation. A pilot programme was initiated in 2008 to share information and arrange joint inspections of API manufacturers. The pilot programme included the EMA, France, Germany, Ireland, Italy, UK, the European Directorate for the Quality of Medicines and Healthcare, the FDA and the Australian Therapeutic Goods Administration and proved successful over a 2-year period. The programme will be continued and other NMRAs encouraged to participate [170].

Developed countries import large quantities of generic drugs and APIs from abroad. It has been estimated that approximately 40% of drugs and 80% of the APIs in pharmaceutical products available in the USA are manufactured elsewhere [171]. Key source countries are China and India. In recognition of the need to ensure regulatory oversight, the FDA has established offices in several countries, including China, India, Costa Rica, Chile, Mexico and South Africa [172]. Activities run from these offices include inspections of facilities and products, training of local regulators and aiding with investigation of adverse incidents, such as suspected contamination.

Parallel importation also carries a risk of substandard drugs being made available as the drugs may be imported via a complex supply chain that is difficult to track. This was highlighted by the recent case of falsified Avastin, thought to have originated in Turkey, which was purchased by medical practices in the USA from foreign or unlicensed suppliers. The purchased drugs were found to contain no API [173].

Most recently, a group of experts in aspects of healthcare provision have proposed the establishment of a global treaty to address the issues of both falsified and substandard medicines. The actions of the treaty would include a legal definition of substandard drugs, establishing track and trace technologies to authenticate medicines, and provision of financial and technical assistance to poorer countries in order to strengthen their medicines regulatory authorities [57].

Human and material resources

A lack of resources to test drug quality is a central issue. A review of occurrences of DEG poisoning noted that in one incident in Haiti, although the pharmaceutical company had the necessary equipment for purity testing, it was not in use and the staff did not know how to use it [47]. A telling press article from Bangladesh reported that the high court had ordered the government to collect and test samples of all the medicines available in 20 specific areas [174]. The authorities had duly collected samples of 174 medicines, but could only test 48 items 'due to shortage of lab equipment'.

Of course, one of the simplest tests is visual inspection of the drugs and their packaging. For example, a case was recently reported in the UK of a patient with malaria that had not resolved with administration of artesunate purchased in Equatorial Guinea. Examination of the outer

packaging of the purchased medication revealed spelling mistakes and design differences, compared with that of the genuine drug, as well as an incorrect company registration number [175]. The tablets were found to contain no API. Reference standards are one of the essential requirements for routine assessment of drug quality and can be purchased from several pharmacopoeias. However, as noted by the USP, limited resources may restrict the use of such standards, and quality testing is then compromised [176]. As part of the Promoting the Quality of Medicines programme, the USP has launched a pilot Technical Assistance Program, which aims to provide practical assistance to regulators in developing countries [176]. Participating countries (initially, Ethiopia, Ghana, Kenya, Senegal and Sierra Leone) will receive, free of charge, a set of pharmaceutical reference standards, documentary standards and technical training to aid in assessing drug quality. The success of the programme will be evaluated after 12 months.

A number of relatively simple and inexpensive tests have been developed for drug testing. Although not necessarily as sensitive or specific as pharmacopoeial methods, they can be used to screen samples quickly. Such techniques include thin-layer chromatography, which has been used as a screening method for a range of suspected substandard drugs, including antituberculosis and antimalarial drugs [23, 177, 178]. Simple colorimetric assays have also been established for some drugs, including the Fast Red TR test that can distinguish the presence of the artemisinin-derived compounds artemether, artesunate and dihydroartemisinin [14, 179, 180]. Dissolution and disintegration tests are also widely used (see Table 3). The Global Pharma Health Fund has developed Minilab®, which incorporates four tests, namely visual inspection, disintegration, colour reaction and thin-layer chromatography tests. A Minilab fits into two suitcases and includes supplies for approximately 1000 assays [181]. The kit has been used for testing the identity of a variety of drugs and may be suitable for initial screening of the quality of imported medicines, as piloted by the Tanzania Food and Drugs Authority [182]. Hand-held Raman and near-infrared instruments are also available for testing of drugs in the field in developing countries, although there are some drawbacks with these approaches [183–186].

The activity of an NMRA or other body assessing drug quality is only as reliable as its staff and, thus, is vulnerable to deficiencies in training and to corruption. There are many levels in the drug production and marketing processes that may be influenced by corruption and lead to substandard drugs entering the market. This may occur, for example, during the construction or equipping of manufacturing facilities, during drug registration or certification, during quality-control checks, including drug testing and site inspections, and during drug procurement [187–189]. One such case was highlighted when the FDA uncovered evidence that a facility in India owned by

Ranbaxy Laboratories had falsified data and test results in approved and pending drug applications on at least two occasions [5, 190]. Provision of adequate training, pay and incentives for staff, as well as greater transparency in all these processes, are required to help alleviate such problems. In Nigeria, for example, as part of a drive to eradicate corruption and to support staff, NAFDAC introduced incentives for its personnel, including training abroad, improved facilities and a better working environment [159].

Improvements in equipment, staff training and implementation of testing and procedures obviously require funding. One possible source is increased drug-registration fees. These fees are substantially lower in developing countries than in developed countries. For example, a review of fees in Latin American countries found that the charges were generally of the order of a few hundred US dollars, but were as low as just US\$6 in Guatemala (cost in 2002) [191]. Other developing countries also charge fees substantially lower than those in developed countries (Table 5). Following a review of NMRA fees in 2002, Kaplan and Laing concluded that for new drug registrations, developing countries could charge between one and five times their per capita gross national product or between US\$17 000 and US\$80 000 for each US\$1000 spent per capita on healthcare, with lower fees for generic drugs [192]. Higher fees could contribute to a more effective regulatory service. However, it is important to strike a balance so that higher costs are not passed on to the consumer, perpetuating the vicious circle in which the production of falsified or low-quality drugs is promoted because of the need for cheaper medicines. Kaplan and Laing emphasize the need for significant additional government funding.

Conclusions

Effective drugs are now available for some of the most prevalent and destructive diseases in the developing world, including tuberculosis, malaria and HIV/AIDS. However, the effectiveness of drugs in treating these diseases, as well as many other illnesses, is compromised by the distribution of substandard drugs. Both branded and generic drugs are affected. Generic formulations offer low-cost options for many drugs, and generic substitution may be mandatory in some countries, but the quality of these drugs must be regulated. In parallel with the resources invested in tackling the problem of deliberately falsified drugs, global effort is required to combat the distribution of low-quality medicines arising through poor manufacturing processes and poor regulatory oversight. Having strong, suitably empowered and well-funded national drug regulatory agencies is essential, and many countries will need help in achieving this goal. Not funding resources to address substandard drug production is a

Table 5

Example drug-registration fees

Country/area	Authority	Date	Drug registration fee	Source
Australia	Therapeutic Goods Administration	2012	Prescription medicines (application + evaluation) New chemical entity: AU\$210 100 New generic product: AU\$80 200	http://www.tga.gov.au/about/fees-current.htm
Europe	European Medicines Agency	2012	€267 400	http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124904.pdf
India	Central Drugs Standard Control Organization	Not known; information currently available on website dated 2007	Imported drug: INR50 000 (approximately US\$913/£576)	http://cdsco.nic.in/html/Sec_122_A.htm
Kenya	Pharmacy and Poisons Board, Ministry of Health	Current information on website dated 2010	Imported: US\$1000. Fully manufactured in Kenya: US\$500 (US\$4000 for Good Manufacturing Practice inspection)	http://pharmacyboardkenya.org/?page_id=401
Nigeria	National Agency for Food, Drug Administration and Control	2011	NGN700 000 (approx. US\$4500/£2700) every 5 years + 5% VAT	http://www.unido.org/fileadmin/user_media/Services/PSD/BEP/Nigeria_Pharma%20Sector%20Profile_032011_Ebook.pdf
Tanzania	Food and Drugs Authority	2011/2012	Foreign manufactured products: application fee US\$500; registration certificate US\$100 per product	http://pharmabiz.com/Services/ExportImport/Countries/Tanzania.aspx
Uganda	National Drug Authority	2010	Foreign manufactured products: US\$500.	http://pharmabiz.com/Services/ExportImport/Countries/Uganda.aspx
USA	Food and Drug Administration	Published in 2012, applicable in 2012/2013	Application requiring clinical data: US\$1 958 800	http://www.gpo.gov/fdsys/pkg/FR-2012-08-01/pdf/2012-18711.pdf

Abbreviations are as follows: INR, Indian rupee; NGN, Nigerian naira; PKR, Pakistani rupee.

false economy; in addition to causing human suffering, the use of substandard drugs can have an enormous economic impact on individuals, families, health providers and states. Governments, drug manufacturers, charities, care providers and patients alike must play their part in ensuring that only drugs of sufficient quality are available for use.

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: Novartis Pharmaceuticals Corporation funded the editorial assistance from Anthemis Consulting Ltd for the submitted work; AJ has received reimbursements and funding from pharmaceutical companies including Astellas, AstraZeneca, Baxter, Novartis, Roche and Sanofi and owns stock in Abbott, AstraZeneca, Pfizer, Roche and Sanofi; DWH has been a speaker for Novartis and Sanofi on issues relating to the impact of drug quality on safety and efficacy.

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