

Review

Substandard medicines in resource-poor settings: a problem that can no longer be ignored

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Summary

The circulation of substandard medicines in the developing world is a serious clinical and public health concern. Problems include under or over concentration of ingredients, contamination, poor quality ingredients, poor stability and inadequate packaging. There are multiple causes. Drugs manufactured for export are not regulated to the same standard as those for domestic use, while regulatory agencies in the less-developed world are poorly equipped to assess and address the problem. A number of recent initiatives have been established to address the problem, most notably the WHO pre-qualification programme. However, much more action is required. Donors should encourage their partners to include more explicit quality requirements in their tender mechanisms, while purchasers should insist that producers and distributors supply drugs that comply with international quality standards. Governments in rich countries should not tolerate the export of substandard pharmaceutical products to poor countries, while developing country governments should improve their ability to detect substandard medicines.

keywords substandard medicines, quality assurance, drug export, contamination, quality standards

Introduction

In October 2004 a doctor working for Médecins Sans Frontières (MSF) in Darfur reported that a local donation of Ringer's lactate infusions was contaminated with a fungal growth. Subsequent investigations revealed that weaknesses in the bottling and quality control procedure during manufacture led to the contamination. The product then passed through three intermediates, including one UN agency, before being offered to relief agencies in Darfur, only one of which reported the problem. The World Health Organization (WHO) and the supplier jointly issued a recall of the contaminated batches. Six months after the recall, however, less than 15% (2200 of 15 000 bottles) of the contaminated product had been located.

This example illustrates the problem of substandard medicines that is commonly confronted by health staff in developing countries. Substandard medicines can have serious clinical and public health consequences: contamination can cause fatal toxicity (O'Brien *et al.* 1998); lack of active ingredient can lead to ineffective treatment and prolonged illness or death (Aldhous 2005); while under dosing of active ingredient carries the additional risk of promoting drug resistance (Laserson *et al.* 2001; Taylor

et al. 2001). However, the problem is very poorly addressed compared to other problems related to quality drug supply such as counterfeit (fake) medicines and inappropriate drug donations (Box 1). This article highlights some of the key concerns derived from MSF's work to assure the quality of medicines for medical relief programmes in less-developed countries, supported by a literature review. Articles were retrieved from a PubMed search for the phrase 'substandard medicines' (1988-present) and further refined with bibliographic search of these articles.

One standard for the rich, another for the poor

In the industrialized world drug regulatory authorities have developed strict standards and controls to ensure drugs are effective and safe. However, in the less-developed world, lack of human and financial resources within the health sector as a whole limits the capacity of drug regulatory agencies, resulting in a suboptimally regulated environment in which substandard drug production can persist without detection.

Circulation of substandard drugs is further encouraged by the fact that drugs manufactured for export are often

Box 1 counterfeit and substandard drugs: distinct definitions for different problems

Counterfeit/fake drugs: Multiple definitions have been proposed for counterfeit drugs, with the common point that they are the result of deliberate criminal activity, 'deliberately and fraudulently mislabelled with respect to identity and/or source' (WHO 2006e).

Counterfeiting can apply to both branded and generic products and may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging (WHO 2003). The United States Food and Drug Administration states that, 'counterfeit drugs are, by definition, outside of the regulatory regime' (Carpenter 2004), while WHO considers counterfeiting as a serious criminal offence that puts human lives at risk and should be combated and punished accordingly (WHO 2006g).

Substandard drugs: According to the WHO, 'Substandard drugs are genuine drug products which do not meet quality specifications set for them.' Similarly, The United States Pharmacopoeia defines a substandard product as a 'legally branded or generic product, but one that does not meet international standards for quality, purity, strength or packaging' (Smine 2002). Simply put, they are as medicines that do not conform to the pharmacopoeial standards set for them (Behrens *et al.* 2002).

not regulated to the same standard as those manufactured for domestic use. An analysis done by the European Union and the French Ministry of Cooperation (Andriollo *et al.* 1997) revealed many problems in the export legislation from European countries to developing countries, including imprecise controls regarding good manufacturing practices for exported products, lack of quality control of products that have not been marketed in Europe, and discordant information between drugs to be exported and drugs for European use (Andriollo *et al.* 1997).

A World Health Assembly Resolution in 1988 requested WHO to 'initiate programmes for the prevention and detection of the export, import, and smuggling of... substandard pharmaceutical preparations' (WHO 1988). More than a decade later the World Health Assembly urged member states to 'establish and enforce regulations that ensure good uniform standards of quality assurance for all pharmaceutical materials and products manufactured in, imported to, exported from, or in

transit through their countries' (WHO 1999a). This was followed by a European Commission directive in 2003 stipulating that 'all medicinal products for human use, including medicinal products intended for export, are to be manufactured in accordance with the principles and guidelines of good manufacturing practices' (European Commission 2003).

However, the reality today is that the quality of drugs for export from developed to developing countries is still determined through a much less rigorous evaluation than for the domestic market (European Commission Humanitarian Aid Department 2006). Efficacy and safety are often not evaluated at all. Drugs destined for international aid and development programmes are also often exempted from regulatory control (Andriollo *et al.* 1997). The expectation is that the recipient country will evaluate the quality of the imported drug. While this may be an acceptable expectation between rich countries, placing this burden of responsibility on countries that do not have the resources to do it is impractical, even exploitative.

The causes

Poor compliance with GMP standards can lead to substandard production. This may be accidental (such as human error) or the result of insufficient resources (expertise, appropriate manufacturing infrastructure, or human and financial resources). Other deliberate causes are often ignored or underestimated. Quality audits of manufacturing sites done by MSF pharmacists (180 sites visited over the last 4 years) have found that manufacturers that regularly pass the most stringent inspections adjust their standards to that of the recipient country. In our observations, parallel productions can exist in the same 'GMP-compliant' facilities: a high standard of production for the strictly regulated markets and for exacting clients such as UN organizations and international aid agencies; an intermediate standard of production for middle-income countries; and a much lower standard for poorly regulated countries.

Quality is not demanded by drug purchasers

Developing country governments often purchase drugs without adequate reference to quality standards. While these are available through WHO publications and via the Internet (US Pharmacopoeia 2008), local authorities in a number of countries have expressed to us their difficulty in accessing these documents and translating this information into clauses for tenders and contracts. Non-governmental organizations working in developing countries also issue drug tenders without applying minimum quality assurance

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procedures (European Commission Humanitarian Aid Department 2006).

Capacity for technical evaluation is limited

The World Health Organisation (WHO) estimates that only one in six countries has fully functional drug regulatory systems (WHO 2004a). Even relatively simple chromatographic or pharmacopeial methods for quality verification (O'Brien *et al.* 1998) are not routinely available (Newton *et al.* 2006) or used effectively (Risha *et al.* 2006). Increasingly, drug registration is a pre-requisite for purchase in resource-limited countries, but authorization to register a medicine is often granted on the basis of a simple review of documents. Quality is impossible to assure in the absence of proper controls that at minimum would include verification of information submitted for evaluation through site inspections, review of batch documentation, and random analysis of drugs supplied (European Commission Humanitarian Aid Department 2006). Regional co-operation to improve technical capacity has been proposed for over 20 years (Jayasena 1985) but little progress has been made.

Limited pharmacovigilance capacity

In the developed world, pharmacovigilance – the detection and prevention of adverse effects and other drug-related problems – is an essential component of any health system, ensuring that problems are quickly detected and resolved. However, the setting up of a functioning pharmacovigilance system, which allows for the rapid communication of problems and recall of harmful drugs is a costly and complicated process that has to compete with many other pressing health system priorities in resource-limited settings.

Where pharmacovigilance systems are weak or non-existent, a higher degree of responsibility is placed on medical staff to guard against adverse effects. Such informal surveillance is further compromised by the acute lack of health staff in most developing countries, where medicines are often prescribed by necessity to patients by health auxiliaries who only receive a very short and basic training that does not emphasize the detection of drug side-effects. Patients for their part often have to travel long distances to receive medication and can rarely afford the time or financial cost of remaining under supervision.

Moreover, many toxic side effects are difficult to detect by clinical observation. For example, the rise in temperature often observed after post-surgery administration of intravenous fluids is usually interpreted to reflect a general degradation of the patient's condition, but we have noted

instances where this is in fact the result of a poor manufacture of the intravenous fluid resulting in contamination with pyrogens.

Drug Regulatory Authorities have recently expressed frustration at not being able to dedicate more resources to post-marketing surveillance (WHO 2006a), all too aware that weak pharmacovigilance limits the detection of substandard drugs, preventing corrective action and supporting their proliferation.

Diminishing number of quality manufacturers for key essential medicines

Pharmaceutical production is profit-driven, and essential medicines are for the most part old molecules that are no longer patent-protected, and therefore generate less profit. For example, penicillins are considered as essential drugs by the WHO (2007a), form part of the United Nations Interagency Emergency Health kit (WHO 2006b), and are still used in significant quantities in developing countries. However, penicillin production has been progressively abandoned in the developed world in favour of more recent and sophisticated antibiotics such as cephalosporins, quinolones, and macrolides. MSF and the UNICEF recently assessed 11 production sites for injectable penicillins. Of these, only two were found to be WHO GMP compliant. The other nine sources are routinely found on the market in Asia and Africa.

Limited understanding of the problem

In general, medical staff have little idea of the risk that substandard products can pose to patients, and there is significant underreporting (Moride *et al.* 1997). Poor reporting in turn reinforces a limited understanding of the problem. Up to half of medicines tested in prevalence surveys were substandard (Table 1), but these surveys are rare, often limited to a few drug classes and test for a narrow set of problems (usually concentration of active ingredient).

Common problems associated with substandard production

Common problems associated with substandard medicines include under or over concentration, contamination, poor quality ingredients, poor stability and packaging problems. Table 2 provides a summary of these problems together with some recent examples.

A study in Nigeria (Taylor *et al.* 2001) found that almost half of randomly sampled antibiotic and antiparasitic drugs did not comply with set pharmacopeial limits. Over and under concentration were equally frequent, and drugs

Table I Summary of major prevalence surveys for substandard drugs

Country	Drugs (<i>n</i> = number of different products tested)	% Substandard	Origin of production	Stated issues	References
Kenya	41 different drugs (<i>n</i> = 277)	46%	Kenya	Failure to comply with quality tests	Kibwage <i>et al.</i> (1992)
	37 different drugs (<i>n</i> = 102)	31%	Imported	Failure to comply with quality tests	Roy (1994)
	Antimalarials (sulphadoxine-pyrimethamine and amodiaquine) (<i>n</i> = 116)	41%	Not stated	Under concentration of active ingredient; dissolution failure	Amin <i>et al.</i> (2005)
	Antimalarials	42%	India, China	Over/under concentration of active ingredient	Atemnkeng <i>et al.</i> (2007)
DRC	Antimalarials (artemisinin derivatives) (<i>n</i> = 7)	14%	Belgium	Over/under concentration of active ingredient	Atemnkeng <i>et al.</i> (2007)
Bangladesh	Paracetamol, ampicillin, cotrimoxazole, vitamin B tablets/injectables (<i>n</i> = 137)	27%	Not stated	Under concentration of active ingredient	Roy (1994)
Myanmar	Amoxicillin, chloroquine, metronidazole, paracetamol, tetracycline, ampicillin, chloramphenicol, rifampicin, co-trimoxazole and ranitidine (<i>n</i> = 212)	16%	21 countries (Asia, Europe, US and Australia)	Under concentration of active ingredient; wrong active ingredient	Wondemagegnehu (1999)
Vietnam	Amoxicillin, chloroquine, metronidazole, paracetamol, tetracycline, ampicillin, chloramphenicol, rifampicin, Diazepam, salbutamol (<i>n</i> = 288)	8%	16 countries (Asia, Europe, Canada and Australia)	Over/under concentration of active ingredient	Wondemagegnehu (1999)
Nigeria	21 antimalarials, antibacterials, antihelmithics and antifungals (<i>n</i> = 581)	48%	12 countries, (including Europe, Nigeria, Egypt, Asia)	Over/under concentration of active ingredient	Taylor <i>et al.</i> (2001)
	Chloroquine, amoxicillin, cotrimoxazole, tetracycline, ampiclox (<i>n</i> = 81)	36%	Not stated	Over/under concentration of active ingredient	Shakoor <i>et al.</i> (1997)
Colombia, Estonia, India, Latvia, Russia, Vietnam	Anti-TB drugs (<i>n</i> = 40)	10%	Not stated	Under concentration of active ingredient	Laserson <i>et al.</i> (2001)
Laos	Ampicillin tetracycline, chloroquine, ASA (<i>n</i> = 366)	46%	Laos, Thailand	Over/under concentration of active ingredient	Stenson <i>et al.</i> (1998)
	Ampicillin tetracycline, chloroquine, ASA (<i>n</i> = 300)	22%	Idem (repeat study)	Over/under concentration of active ingredient; over concentration of non-active ingredient; disintegration	Syhakhang <i>et al.</i> (2004)

Table 1 (Continued)

Country	Drugs (<i>n</i> = number of different products tested)	% Substandard	Origin of production	Stated issues	References
Thailand	Chloroquine, amoxicillin, cotrimoxazole, tetracycline, ampiclox (<i>n</i> = 15)	40%	Not stated	Over/under concentration of active ingredient	Shakoor <i>et al.</i> (1997)
Tanzania	Antimalarials (<i>n</i> = 33)	36%	Cyprus, Tanzania, India, Kenya	Under concentration of active ingredient; dissolution failure	Minzi <i>et al.</i> (2003)
Cambodia	Antimalarials (<i>n</i> = 451)	27%	16 countries cited	Under concentration of active ingredient; dissolution failure	Lon <i>et al.</i> (2006)
Cameroon, Madagascar, Chad	Antibiotics, analgesics, antiparasitics (<i>n</i> = 429)	18%	Not stated	Over/under concentration of active ingredient; no active ingredient (20%); contamination	ReMeD (1995)
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	Antimalarials chloroquine and sulphadoxine-pyrimethamine (<i>n</i> = 278)	23% Range: 9% Sudan 41% Mali	Local and Imported	Under concentration	Maponga and Ondari (2003)

ReMeD, Réseau Médicaments et Développement.

labelled as originating from developed countries (Belgium, Holland, Switzerland and the UK) had similarly imprecise contents as those labelled as originating from less-developed countries.

Contamination is a recurrent problem, and can have fatal consequences, particularly with intravenous products. In MSF's experience, microbial contamination of injections and infusions is often the result of poor sterilization management, obsolete equipment, inappropriate production environment or too short sterilization cycles (to cut costs). It can also be the result of poor quality packaging materials.

Contamination of active pharmaceutical ingredient (API) with residues of solvents used in the synthesis or other toxic impurities is another frequent and important concern. The quality of the API is one of the major determinants of quality for all pharmaceuticals. However, it is also here that compromise can lead to the greatest cost saving as APIs can represent over 80% of the price of finished products (Pinheiro *et al.* 2006).

An example is rifampicin, a key agent in the first line treatment against tuberculosis. Production of the API is complex and can lead to forms of the molecule which are not equally soluble and therefore of variable bioavailability. This can have dramatic consequences in terms of public health, since poorly effective drugs can lead to the development of drug resistance. This problem has been

noted by WHO which has published guidelines for the purchase of rifampicin-containing products (WHO 1999b; Newton *et al.* 2006). Nevertheless, MSF has been confronted with several sources of rifampicin (both single ingredient and fixed-dose combination tablets) that are registered, marketed and used in many African and Asian countries but have no proof of efficacy.

Non-active ingredients (excipients) can pose as much as a threat as active ingredients, perhaps more so given that manufacturers are generally not required to provide any information at all on excipients. One of the most frequently cited cases of substandard drugs – the death of 88 children in Haiti after ingestion of paracetamol liquid – was the consequence of a poor quality excipient. It is not clear whether this was the result of counterfeiting or not (O'Brien *et al.* 1998).

Product stability is another parameter that has a direct influence on the quality and efficacy of the medicine. Pharmaceutical degradation is generally accelerated by heat and humidity and WHO recommends stability testing in tropical conditions (WHO 2006c), but this not always done (Omer 1990; Arya 1995). Artesunate, an essential antimalarial drug, is extremely sensitive to heat and humidity. Stable formulations of Artesunate are difficult to produce (the quality of the packaging material is critical) (Fawaz & Millet 2006) while co-formulations of Artesunate with other antimalarials are even more

Table 2 Different categories of substandard medicines

Issue	Example	Country	Origin of product	Reported
Over concentration	TB drugs	Chad	Europe (6 countries), Kenya, India	ReMeD*
	Antimalarials	Kenya, DRC		Atemnkeng <i>et al.</i> (2007)
Under concentration	TB drugs	Colombia, Estonia, India, Latvia, Russia and Vietnam	Not stated	Laserson <i>et al.</i> (2001)
Irregular filling of vials	Paracetamol, ampicilin, co-trimoxazole	Bangladesh	Not stated	Stenson <i>et al.</i> (1998)
	Over or subdosed Thiopental Sodium vials	Belgium (MSF procurement centre warehouse)	Cyprus	Company alert (1998)*
Contamination	Microbial contamination of distilled water	MFS procurement in Europe	Hungary	MSF (1999)*
	Detergent contamination of i.v. fluids	MSF procurement centres in Europe	UK	AFSSAPS (French DRA) and company alert (2003)*
	Fungal contamination of i.v. fluid bags	MSF procurement centres in Europe)	India	MSF (2004)*
	Black particles in SSG (Pentostam) vials	Sudan UK	Switzerland	MHRA (UK DRA) and company alert (2006, 2007)*
Mislabelling (not counterfeit)	Ethyl methane sulphonate (EMS) contamination of Nelfinavir API and formulations	EU and Africa		EMEA (2007)*
	Paracetamol tablets labelled as co-trimoxazole	Democratic Republic of Congo	India	MSF (2007)*
Problems with active ingredient	Variable solubility and bioavailability of active ingredients of Rifampicin		Not stated	MSF (2006)*
	Morphology of the active ingredient (furosemide) affecting the dissolution	France	France, Kyghizstan, Kenya	Cavenaghi (1989), Bauer <i>et al.</i> (2002)
Problems with excipient	Glycerin contaminated with diethylene glycol used in 15 000 bottles of paracetamol liquid caused death of 88 children	Haiti	Glycerin imported from China via Europe	O'Brien <i>et al.</i> (1998)
	Diethylene glycol used instead of propylene glycol in a cough syrup killed more than 30 children in India	India	India	Singh <i>et al.</i> (2001)
	Diethylene glycol used in a cough syrup killed 21 persons in Panama	Panama	Panama	FDA (2006)*
Poor stability	Changes in colour: amoxicillin and clavulanic acid tablets	Georgia	Cyprus	MSF (2006)*
	Change in smell: erythromycin tablets (two sources)	Armenia	Malta, India	MSF (2004)*
	Change in consistency: crystalization in SSG vials	Sudan	India	MSF (2004)*
	Loss of potency (measles vaccine)	Nigeria	UNICEF	Onoja <i>et al.</i> (1992)
	Loss of active ingredient: ergometrine injections	Zimbabwe	Not stated	Nazerali and Hogerzeil (2003)

Table 2 (Continued)

Issue	Example	Country	Origin of product	Reported
Packaging problems	I.v. fluid bottles contaminated	Kenya	India	MSF (2002, 2003)*
	Microcracks caused by wrong bottle shape, poor quality plastic or rough transportation	Sudan	India	MSF (2004)*
	TB drugs moisture-damaged due to water-permeable blister packs	India	India	Singh and Mohan (2003)
Unsatisfactory dissolution profiles	Higher dissolution rate of active ingredient in antidiabetic drugs (resulting in higher and quicker peak in blood and toxicity)	France	Cyprus, UK, Kenya	Ba <i>et al.</i> (2005)
	Poor dissolution of antimalarials	Kenya	Cyprus, Tanzania, India, Kenya	Amin <i>et al.</i> (2005)
		Tanzania		Minzi <i>et al.</i> (2003)

DRA, drug regulatory authority; ReMeD, Réseau Médicaments et Développement.

*Unpublished reports.

challenging as these latter molecules can increase the instability of Artesunate. MSF has found it difficult to obtain consistent stability data from producers, although this is crucial information for guaranteeing the efficacy of the product and avoid the emergence of resistance. When stability studies are performed they often do not adhere to WHO guidelines, especially for the testing in zone IV (tropical) conditions.

Efforts to address the problem

Substandard medicines represent a far larger risk to public health than counterfeit medicines. However, with some exceptions (Shakoor *et al.* 1997; Taylor *et al.* 2001; Behrens *et al.* 2002; Kelesidis *et al.* 2007; Newton *et al.* 2008) substandard and counterfeit drugs are regularly conflated and confused (Verduin-Muttiganzi & Verduin-Muttiganzi 1998; Laserson *et al.* 2001; Po 2001; Figueras *et al.* 2002; Wertheimer *et al.* 2003; Rassoool 2004; Amin *et al.* 2005; Videau 2006; Atemnkeng *et al.* 2007).

The problem of counterfeit medicines is serious, and indeed has been described as 'epidemic' in the case of artesunate in South-East Asia (Newton *et al.* 2008). Determining whether a medicine is counterfeit is problematic (Behrens *et al.* 2002), yet the few published reports that did differentiate between the two problems have found that the majority of poor quality drugs were genuine, but substandard drugs, and not the result of counterfeiting (Wondemagegehu 1999; Syhakhang *et al.* 2004; Atemnkeng *et al.* 2007). One WHO study (Syhakhang *et al.* 2004) found that almost all (18/19) poor quality

medicines were genuine products, yet this study has been cited elsewhere by WHO as evidence of counterfeiting (Maponga & Ondari 2003).

Because substandard drugs are frequently portrayed as a consequence of counterfeiting, it is hardly surprising that the majority of international attention and action is directed at the latter. This is partly because counterfeit drugs undermine the markets of pharmaceutical companies who put significant energy into tackling the problem. As a result, WHO is promoting a global approach to combat the problem of counterfeit medical products through reporting procedures and enhanced access to information (WHO 1999c), and has launched a taskforce (International Medical Products Anti-Counterfeiting Taskforce) against counterfeit drugs (WHO 2006d). The Pan American Health Organisation works collaboratively with the United States against counterfeits (US Pharmacopeia 2008) and the International Conference of Drug Regulatory Authorities, promoted by WHO, has incorporated the problem of drug counterfeiting in the agendas of its meetings since 1992 (WHO 2004b).

In contrast, there is little commercial incentive to invest in reducing the proliferation of substandard medicines, and this remains a poorly quantified and ill addressed problem. When actions are taken, resources are often focused on ad hoc quality controls while what is in fact needed is a strong quality assurance framework to ensure that the products produced are of an acceptable quality in the first place (WHO 2003a). Quality control is part of quality assurance and investing in quality control only makes sense if a strong quality assurance system is in place.

The purchase of medicines in developed and developing countries must be based on a technical evaluation and approval of the manufacturing site and the product itself. One important step in this direction is the establishment of the WHO pre-qualification programme (mednet3.who.int/prequal/) that has had a major impact on the quality of medicines across the developing world, providing a benchmark of quality for resource-limited countries in an otherwise chaotic environment.

The pre-qualification programme mobilizes a high level of technical expertise for the evaluation of manufacturing sites (GMP inspections) and assessment of product dossiers. The Global Fund and other major donors refer to the list of WHO pre-qualification products and encourage countries to purchase them preferentially. In 2005 four African countries refused to register a US Food and Drugs Administration antiretroviral combination therapy because the drug had not been pre-qualified by the WHO pre-qualification project (Donnelly 2005). To support the pre-qualification project, WHO has also invested significant resources to build capacity in developing countries through GMP training for local inspectors and pharmacovigilance workshops in the context of HIV/AIDS programmes.

Until recently the pre-qualification project only covered medicines for HIV/AIDS, TB, and malaria. Drugs for reproductive health and *avian* influenza have recently been added. However, insufficient resources mean that even within this narrow scope it is limited in the speed of the review and quantity of drugs it is able to process. Nevertheless, the WHO pre-qualification programme has given a clear signal to producers, distributors, regulators, and health providers that essential quality standards can and should be applied, and that the proliferation of substandard products is not an inevitability.

Two other initiatives have recently been launched by WHO. The Model Drug Registration Package (WHO 2007b) aims to improve understanding of drug regulatory requirements and facilitate collaboration and technical exchange between drug regulatory authorities in developed and developing countries, while the Model Quality Assurance System (MQAS) (WHO 2006e) provides guidelines for procurement agencies on quality assurance and stimulates exchange and collaboration between drug regulatory agencies in developed and developing countries. Unfortunately, in our experience very few procurement agencies comply with the MQAS, while few purchasers have the capacity to assess the compliance of their procurement agents with the MQAS.

In order to fill the current gap between what these new initiatives can currently deliver and the immediate need to support medical programmes with a broad range of drug requirements, MSF developed a qualification system in

Box 2 Outline of MSF's qualification system

Manufacturing site assessment for GMP

compliance: Sites approved in the previous 2 years by internationally recognized inspectors* are approved *de facto* by MSF. Other sites of potential interest are audited by a consultant GMP expert.

Product evaluation: Once WHO GMP compliance is established, MSF pharmacists undertake product evaluation using classic quality indicators organizing in the following categories: country of origin/countries of registration of the product; stability studies; finished product specifications; active pharmaceutical ingredients; packaging/labelling/patient information; GMP status of the manufacturing site; and proof of therapeutic equivalence when required.

Decision process: On the basis of this information products are then approved or rejected for use in MSF programmes. This decision is communicated to the producer.

No quality source identified: There are sometimes cases where the technical information provided by the producers is not sufficient to validate the product. MSF's primary mandate is to provide emergency medical assistance and the drug quality assessment cannot be detrimental to the ability to respond to emergency needs. A balanced risk-benefit assessment is done by the Medical Directors and, if the product is to be accepted, a temporary exceptional authorization to supply is granted. The result of the evaluation is available for the National Drug Regulatory Authorities (if they exist).

*Member inspectorates of the Pharmaceutical Inspection Co-operation Scheme, the International Conference on Harmonization or the WHO Pre-qualification project.

2003 to ensure that the drugs purchased by its procurement centres are in line with WHO standards. MSF's qualification system draws on existing international procedures, standards and specifications (WHO 1997, 1999d, 2004c, 2006f, 2007b, Maponga & Ondari 2003) to assess specific product dossiers and manufacturing sites (Box 2). This qualification process is only undertaken for drugs not already validated by stringent regulatory agencies or the

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WHO pre-qualification project. The work is done by MSF pharmacists with the assistance of external experts for particular areas that require specialized assistance such as bioequivalence studies or GMP audits.

Discussion

Significant resources have been devoted to tackle counterfeit medicines, but very little specific attention has been given to the far more serious and widespread problem of substandard medicines. This is partly a consequence of the poor differentiation made between these two distinct problems. However, reducing the problem of substandard medicines to a consequence of counterfeiting skews resources towards legal action alone, complicating efforts to define targeted strategies to specifically address the problem of the substandard medicines. The focus of attention should rather be on the detection and removal of poor quality medicines, whether they are counterfeit or not, while at the same time assisting legitimate manufacturers to improve the quality of their pharmaceutical production.

The limited resources available for the development of efficient pharmacovigilance systems in developing countries compound the problem. Because the consequences of substandard medicines, both on individuals and on public health, often go unreported, there is no stimulus to intervene.

The pre-qualification programme has recently been expanded but capacity remains limited, and the majority of essential drugs remain outside of the scope of the programme and are still purchased without a proper evaluation. Other recent initiatives by WHO are important but remain financially fragile; moreover, these measures will be only successful if other actors involved in drug procurement assume their responsibilities.

Donors have an important role to play by strengthening quality clauses based on WHO standards in the tender mechanisms they impose on non-governmental organizations. Likewise, drug purchasers (NGOs, international organizations, charities, and national purchase centres in resource-limited countries) should assume their responsibility towards protecting patients' health and insist that producers and distributors supply drugs that meet WHO standards. Quality assurance is a mandatory preliminary to drug purchases in the West, and there is no rationale for this procedure to be any different when drugs are exported to poor populations. Governments could act now to reduce this problem by granting export authorization only to pharmaceutical products that comply with the WHO standards for quality, efficacy and safety.

Developing country governments can make important improvements with minor investments, particularly by making more use of technical resources that are already available from WHO and other organizations. This would be further enhanced through regional collaboration.

The reality today is that health care providers in resource-poor settings are finding it increasingly difficult to find sustainable and affordable sources of essential quality drugs. Confronted with situations where no quality assured product is available, they must make the impossible calculation of weighing the risk of not treating against that of using a drug whose quality and safety is unknown. This unacceptable situation will continue and in all likelihood worsen unless those responsible assume their responsibilities. Acknowledging the problem would be a good place to start.

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