Tropical Medicine and International Health doi:10.1111/j.1365-3156.2012.03076.x

VOLUME 17 NO 11 PP 1412–1416 NOVEMBER 2012

Editorial

# Poor-quality medical products: time to address substandards, not only counterfeits

**Raffaella M. Ravinetto[1], Marleen Boelaert[2], Jan Jacobs[1,3], Corinne Pouget[4] and Christophe Luyckx[2]**

1 *Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium*
2 *Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium*
3 *Department of Medical Microbiology, Faculty of Health and Life Sciences, Mastricht, The Netherlands*
4 *Consultant, Institute of Tropical Medicine, Antwerp, Belgium*

**keywords** quality of medicines, quality of IVDs, medicines regulation, substandard, counterfeit, World Health Assembly

The rapid globalisation of the pharmaceutical market that characterised the two last decades has led to a situation of *multiple standards* (Caudron *et al.* 2008): the quality of medicines is not uniform worldwide, but largely depends on the level of income (Newton 2010) and regulation (Editorial, 1852; World Health Organization, 2010; Nishtar 2012) in the country of destination. Poor-quality medicines are generally cathegorised as either *counterfeits*, which are deliberately and fraudulently mislabelled with respect to identity and/or source (http://www.who.int/mediacentre/factsheets/fs275/en/), or *substandards*, which according to the WHO definition of 2010 are genuine medicines produced by the manufacturers authorised by the National Medicine Regulatory Authority (NMRA) but do not meet quality specifications set by national standards (http://www.who.int/medicines/services/counterfeit/faqs/06/en/index.html).

Over recent years, a growing number of global initiatives have been launched to fight the illegal counterfeit medicines (Declaration of Rome, 2006; 13th International Conference of Drug Regulatory Authorities, 2008; Appel de Cotonou contre les faux médicaments, 2009; Council of Europe Convention, 2011), which have become quite a well-known issue, also for the general public and lay press. Conversely, substandards have remained poorly or not addressed, despite being a more widespread problem, highly prevalent in resource-poor settings (Caudron *et al.* 2008; Newton 2010) and at least as dangerous as counterfeits.

Between 2008 and 2011, the World Health Assembly (WHA) faced persistent difficulties to reach an agreement for adopting a resolution on this matter. However, the 65th WHA approved a resolution on a new 'Member State mechanism' (i.e. an intergovernmental mechanism, open to all WHO Member States), proposing international collaboration on 'substandard, spurious, falsely-labelled, falsified or counterfeit (SSFFC) medical products'. The explicit goal of the Member State mechanism will be 'to promote the prevention and control of SSFFC medical products and associated activities, to protect public health and promote access to affordable, safe, efficacious and quality medical products'. This creates an opportunity to tackle the problem in a comprehensive, patient-centered approach. But will the Member State mechanism be able to turn the tide? What is the extent of SSFFC, and how should they be approached and fought?

## Quality of medicines: a cross-cutting issue

Even if surveys on quality are not generally conducted according to harmonised methods (Newton *et al.* 2009), there is evidence that poor-quality medicines are widespread in poor countries, with serious and often undetected consequences for individuals and for public health. Problems have been mainly documented in the field of malaria (OMS, 1995; Maponga & Ondari 2003; Minzi *et al.* 2003; Abdo-Rabbo *et al.* 2005; Amin *et al.* 2005, 2007; Alfadl *et al.* 2006; Atemnkeng *et al.* 2007; Gaudiano *et al.* 2007; Bate *et al.* 2008; Kaur *et al.* 2008; Tipke *et al.* 2008; Leslie *et al.* 2009; WHO, 2011a; Gaurvika *et al.* 2012), most likely because physicians' and decision-makers' awareness has significantly grown because of the spectacular raise in resistance to the traditional molecules. To a minor extent, quality has been investigated and problems have been documented in other therapeutic fields, including tuberculosis (Laserson *et al.* 2001; Laing *et al.* 2004; WHO, 2011b), infectious disease (The USP Drug Quality and

Information Program, 2004; Kelisidis *et al.* 2007), neglected diseases (Sundar *et al.* 1998; Dorlo *et al.* 2012), chronic diseases (Laroche *et al.* 2005; Arie 2012) and others (Eichie *et al.* 2009), as well as in non-disease-specific surveys (Shakoor *et al.* 1997; WHO 1999; Taylor *et al.* 2001). Tragically, the presence of poor-quality medicines often comes to light only *after* the observation of increased resistance patterns or abnormal morbidity and mortality rates, as it recently happened in Bangladesh (Dorlo *et al.* 2012) and in Pakistan (Arie 2012). To date, the resources mobilised for assuring the quality of HIV-AIDS, malaria and tuberculosis medicines (http://apps.who.int/prequal/default.htm; http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/#General; http://www.fda.gov/InternationalPrograms/FDABeyondOurBorders ForeignOffices/AsiaandAfrica/ucm119231.htm) resulted in encouraging results for the medicines covered by international mechanisms such as the WHO prequalification (World Health Organization, 2007; WHO, 2011a,b). No comparable mechanisms exist to ensure the quality of the other essential medicines; nonetheless, poor-quality medicines are not limited to specific diseases, and even simple anti-febrile and anti-cough medicines may cause death if contaminated (Geiling & Cannon 1938; Okuonghae *et al.* 1992; Hanif *et al.* 1995; Woolf 1998; Singh *et al.* 2001; Rentz *et al.* 2008; Abubukar *et al.* 2009).

Remarkably, similar concerns about a north–south quality gap, leading to serious consequences for the health of vulnerable populations, have been expressed about *in vitro* diagnostics and medical devices, where substandards seem to be a more widespread problem than counterfeits (Mori *et al.* 2011).

## Inadequate definitions?

The 2010 WHO definition of substandard medicines – 'genuine medicines produced by the manufacturers authorised by the NMRA which do not meet quality specifications set for them by national standards' – (http://www.who.int/medicines/services/counterfeit/faqs/06/en/index.html) differs from the previous one[1] in that the reference to quality specifications set in official pharmacopoeias has been replaced by the reference to quality specifications set by national standards, without taking into account that according to the WHO itself, only approximately 20% of countries have fully operational regulatory mechanisms for medicines. Of the remaining countries, 50% have NMRAs of varying capacity and 30% have either no or very limited capacity for medicine regulation (African Medicines Regulatory Harmonization Initiative, 2008), for example, limited capacity to obtain the minimal information needed to thoroughly assess products' dossiers before registration. In the case of countries with underresourced NMRAs, setting the national standard as reference leads to a normative framework that *de facto* accepts a multiplicity of standards, including inadequate standards. This contrasts with the previous definition, which promoted the reference to the internationally recognised and harmonised standards of official pharmacopoeias. The inadequacy of the current definition of substandards enables many manufacturers to sell poor-quality medicines with no risk to be sanctioned, just because these products have been registered by NMRAs with limited capacity. The current *status quo* furthers the interests of companies with poor technical capacity or with poor ethics, but it certainly does not serve the interests of the patients.

## Opportunities and threats for the Member State mechanism

The difficulties that caused the delay of agreement at WHA level were mainly because of the sometimes almost exclusive emphasis on 'counterfeits', and to the tensions between the 'intellectual property approach' and the 'public health approach' (Newton *et al.* 2011). A constructive dialogue for developing measures that ensure universal access to medicines of proven quality is now rapidly required to achieve the human right to health (Universal Declaration of Human Rights 1948, art. 25) as well as one of the Millenium Goals (target 8.E, 'in cooperation with pharmaceutical companies, provide access to affordable essential medicines in developing countries').

As the SSFFC definition encompasses medicines, vaccines, medical devices and *in vitro* diagnostic tests, the new Member State mechanism has now the opportunity to shape evidence-grounded policies for protecting vulnerable men, women and children from the plague of poor-quality medical products as a whole, thus addressing the problem comprehensively rather than product by product or disease by disease, and without prioritising counterfeits over substandards. This may only be achieved

[1]They are genuine drug products that do not meet quality specifications set for them. The term 'substandard' is used to describe the quality status of genuine drugs produced by legitimate manufacturers. Normally, for each drug product that a manufacturer produces, he/she sets the quality standards or specifications. Such specifications are also published in official pharmacopoeias such as the United States Pharmacopoeia, the European Pharmacopoeia and the WHO International Pharmacopoeia. If a drug, upon laboratory testing in accordance with the specifications, it claims to comply with, fails to meet the specifications, it is classified as substandard.

by a complex set of measures that are needed to *prevent* the appearance of poor-quality medical products and that include:

- Strengthening the national *and* international regulatory oversight – without putting the responsibility exclusively on the authorities in the 'territory of use';
- Increasing transparency on quality information;
- Defining quality specifications based on WHO standards (WHO, 2011c; http://www.who.int/medicines/areas/quality_safety/en/);
- Adapting the procurement policies of all the major donors and procurement agencies, to promote a uniform reference to WHO standards (WHO, 2011c; http://www.who.int/medicines/areas/quality_safety/en/).

It is hoped that the Member State mechanism will manage to overcome those ideological, economical and commercial interests that have so dramatically delayed this issue at the WHA over the last six years. The interest of the patient and the protection of his/her health should be central. Any other considerations are peripheral.

## Acknowledgements

We wish to thank Jacques Pinel and Bruno Gryseels, for inspiring and supporting us in the development of the ideas expressed in this article.

## References

Abdo-Rabbo A, Bassili A & Atta H (2005) The quality of antimalarials available in Yemen. *Malaria Journal* **4**, 28. http://www.malaria journal.com/content/4/1/28

Abubukar A, Awosanya E, Badaru O *et al.* (2009) Fatal poisoning among young children from diethylene glycol-contaminated acetaminophen – Nigeria, 2008–2009. *Morbidity and Mortality Weekly Report* **58**, 1345–1347.

Alfadl AA, Abdoon S, Elamin M & Elnabi NG (2006) Quality of antimalarial drugs in Sudan: results of post-marketing surveillance. *Sudanese Journal of Public Health* **1**, 108–111.

Amin AA, Snow RW & Kokwaro GO (2005) The quality of sulphadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. *Journal of Clinical Pharmacy and Therapeutics* **30**, 559–565.

Amin AA & Kokwaro GO (2007) Antimalarial drug quality in Africa. *Journal of Clinical Pharmacy and Therapeutics* **32**, 429–440.

Appel de Cotonou contre les faux médicaments (2009) Fondation Chirac. http://www.fondationchirac.eu/programmes/acces-aux-medicaments/mobilisation-internationale-contre-trafic-faux-medicaments/ (Accessed on August 6 2012).

Arie S (2012) Contaminated drugs are held responsible for 120 deaths in Pakistan. *British Medical Journal* **344**, e951.

Atemnkeng MA, Katelijne De C, Jacqueline P-V (2007) Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and R Congo. *Tropical Medicine and International Health* **12**, 68–74.

Bate R, Coticelli P, Tren R & Attaran A (2008) Antimalarial drug quality in the most severely malarious parts of Africa – a six country study. *PLoS One* **3**, e2132.

Caudron J-M, Ford N, Henkens M, Mace C, Kiddle-Monroe R & Pinel J (2008) Substandard medicines in resource-poor settings: a problem that can no longer be ignored. *Tropical Medicine and International Health* **13**, 1062–1072.

Declaration of Rome (2006) Conclusions and recommendations of the WHO "combating counterfeit drugs: building effective international collaboration" International Conference, Rome, Italy 16–18 February 2006. http://www.who.int/medicines/counterfeit_conference/en/index.html

Dorlo TPC, Eggelte TA, Schoone GJ, de Vries PJ & Beijnen JH (2012) A poor-quality generic drug for the treatment of visceral Leishmaniasis: a case report and appeal. *PLoS Neglected Tropical Diseases* **6**, e1544.

Editorial (1852) Drug regulation in India – the time is ripe for change. *The Lancet* **2012**, 379.

Eichie FE, Arhewoh IM & Ezeobi OC (2009) *In-vitro* evaluation of the pharmaceutical quality of some ibuprofen tablets dispensed in Nigeria. *African Journal of Pharmacy and Pharmacology* **3**, 491–495. http://www.academicjournals.org/ajpp

Gaudiano MC, Di Maggio A, Cocchieri E *et al.* (2007) Informal medicine market in Congo, Burundi and Angola: counterfeit and sub-standard antimalarials. *Malaria Journal*, **6**, 22.

Gaurvika M, Nayyar L, Breman JG, Newton PN & Herrington J (2012) Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *The Lancet Infectious Diseases* **12**, 488–496.

Geiling EMK & Cannon PR (1938) Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning. A clinical and experimental correlation: final report. *Journal of the American Medical Association* **111**, 919–926.

Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ Jr & Bennish ML (1995) Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *British Medical Journal* **311**, 88–91.

Kaur H, Goodman C, Thompson E, Thompson KA, Masanja I *et al.* (2008) A nationwide survey of the quality of antimalarials in retail outlets in Tanzania. *PLoS One* **3**, e3403.

Kelesidis T, Kelesidis I, Rafailidis PI & Falagas ME (2007) Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence. *Journal of Antimicrobial Chemotherapy* **60**, 214–236.

Laing R, Vrakking H & Fourie B (2004) Quality and stability of TB medicines: let the buyer beware! *The International Journal of Tuberculosis and Lung Disease* **8**, 1043–1044.

Laroche ML, Traore H, Merle L, Gaulier JM, Viana M & Preux P-M (2005) Quality of Phenobarbital solid-dosage forms in the

urban community of Nouakchott (Mauritania). *Epilepsia* **46**, 1293–1296.

Laserson KF, Kenyon AS, Kenyon TA, Layloff T & Binkin NJ (2001) Substandard tuberculosis drugs on the global market and their simple detection. *The International Journal of Tuberculosis and Lung Disease* **5**, 448–454.

Leslie T, Kaur H, Mohammed N, Kolaczinski K, Ord RI & Rowland M (2009) Epidemics of Plasmodium Falciparum malaria involving substandard antimalarial drugs, Pakistan 2003. *Emerging Infectious Diseases* **15**, 1753–1759.

Maponga C & Ondari C (2003) *The Quality of Antimalarials. A Study in Selected African Countries*. (WHO/EDM/PAR/2003) Department of Essential Drugs and Medicines Policy, World Health Organization, Geneva, Switzerland. http://apps.who.int/medicinedocs/en/d/Js4901e/.

Minzi OMS, Moshi MJ, Hipolite D *et al.* (2003) Evaluation of the quality of amodiaquine and sulphadoxine/pyrimethamine tablets sold by private wholesale pharmacies in Dar Es Salaam Tanzania. *Journal of Clinical Pharmacy and Therapeutics* **28**, 117–122.

Mori M, Ravinetto R & Jacobs J (2011) Quality of medical devices and in vitro diagnostics in resource-limited settings. *Tropical Medicine & International Health* **16**, 1439–1449.

Newton PN, Green MD & Fernández FM (2010) Impact of poor-quality medicines in the 'developing' World. *Trends in Pharmacological Sciences* **31**, 99–101.

Newton PN, Lee SJ, Goodman C *et al.* (2009) Guidelines for field surveys of the quality of medicines: a proposal. *PloS Medicine* **6**, 252–257.

Newton PN, Amin AA, Bird C, Passmore P, Dukes G *et al.* (2011) The primacy of public health. Considerations in defining poor quality medicines. *PLoS Medicine* **8**, e1001139.

Nishtar S (2012) Pakistan's deadly cocktail of substandard drugs. *The Lancet* **379**, 1084–1085.

Okuonghae HO, Ighogboja IS, Lawson JO & Nwana EJC (1992) Diethylene glycol poisoning in Nigerian children. *Annals of Tropical Paeditrics* **12**, 235–238.

OMS (1995) La qualité des médicaments sur le marché pharmaceutique africain. Etude analytique dans trois pays: Cameroun, Madagascar, Tchad. Programme d'Action pour les Médicaments Essentiels, OMS. http://apps.who.int/medicinedocs/fr/d/Js2212f/.

Rentz D, Lewis L, Mujica OJ *et al.* (2008) Outbreak of acute renal failure in Panama in 2006: a case-control study. *Bulletin of the World Health Organization* **86**, 749–756. Available at WHO website.

Shakoor O, Taylor RB & Behrens RH (1997) Assessment of the incidence of substandard drugs in developing countries. *Tropical Medicine and International Health* **2**, 839–845.

Singh J, Dutta AK, Khare S *et al.* (2001) Diethylene glycol poisoning in Gurgaon, India. *Bulletin of the World Health Organization* **79**, 88–95.

Sundar S, Sinha PR, Agrawal NK *et al.* (1998) A cluster of cases of severe cardiotoxicity among kala-azar patients treated with a high-osmolarity lot of sodium antimony gluconate. *American Journal of Tropical Medicine and Hygiene* **59**, 139–143.

Taylor RB, Shakoor O, Behrens RH *et al.* (2001) Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. *The Lancet* **357**, 1933–1936.

The USP Drug Quality and Information Program (2004) A review of drug quality in Asia with focus on anti-infective. http://pdf.usaid.gov/pdf_docs/PNADH154.pdf

Tipke M, Diallo S, Coulibaly B *et al.* (2008) Substandard antimalarial drugs in Burkina Faso. *Malaria Journal* **7**, 95.

WHO (1999). *Counterfeit and Substandard Drugs in Myanmar and Viet Nam. Report of a study carried out in cooperation with the Governments of Myanmar and Viet Nam. E. Wondemagegnehu, WHO Essential Drugs and Other Medicines*. (WHO/EDM/QSM/99.3) WHO, Geneva.

WHO (2011a) Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. WHO (Quality Assurance and Safety of Medicines, Department of Essential Medicines and Pharmaceutical Policies), Geneva. http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf

WHO (2011b) WHO quality assurance and safety: medicines, essential medicines and pharmaceutical policies. Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union. Health Technologies and Pharmaceuticals, WHO Regional Office for Europe, Geneva. http://apps.who.int/medicinedocs/documents/s19053en/s19053en.pdf

WHO (2011c) WHO technical report series 961: WHO expert committee on specifications for pharmaceutical preparations, forty-fifth report. http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf

Woolf AD (1998) The haitian diethylene glycol poisoning tragedy. *Journal of the American Medical Association* **279**, 1215–1216.

World Health Organization (2007) *Quality Assurance and Safety: Medicines. Medicines Policy and Standards*. Survey on the quality of antiretroviral medicines circulating in selected African countries. (WHO/PSM/QSM/2007.9) WHO, Geneva. http://www.who.int/medicines/publications/ARV_survey.pdf

World Health Organization (2010) *Assessment of Medicines Regulatory Systems in Sub-Saharan African Countries: An Overview of Findings from 26 Assessment Reports* WHO, Geneva.

WHO Fact sheet No 275. http://www.coe.int/t/DGHL/Standard-Setting/MediCrime/Default_en.asp

WHO frequently asked questions. http://www.who.int/medicines/services/counterfeit/faqs/06/en/index.html

Council of Europe Convention on the counterfeiting of medical products and similar crimes involving threats to public health, 28th October 2011. http://www.coe.int/t/DGHL/Standard Setting/MediCrime/Default_en.asp (Accessed on August 6 2012).

 

13th International Conference of drug regulatory authorities, strategies to fight counterfeit medicines (2008). *WHO Drug Information* **22**, 262–263. http://www.who.int/medicines/publications/druginformation/issues/DrugInfo08vol22-4.pdf (Accessed on August 6 2012).

African Medicines Regulatory Harmonization Initiative (AMRHI): a WHO concept paper (2008). *WHO Drug Information* **22**, 182–190.

**Corresponding Author** **Raffaella M. Ravinetto**, Clinical Sciences Department, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium. Tel.: 0032 (0) 3 247 6625; Fax: 0032 (0) 3 247 6647; E-mail: rravinetto@itg.be.